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Investigating the Epidemiology of Medication Errors in Adults using Electronic Health Records in Riyadh, Saudi Arabia

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Abstract

Introduction: The Harvard Medical Practice (Study II) identified medications as the most common source of injury resulting from medical care. The subsequent Institute Of Medicine (IOM; now renamed as the National Academy of Medicine) report *"To Err Is Human: Building a Safer Health System"* brought considerable national and international attention to the problem of errors in hospitals. Given that medication errors and error-related adverse drug events (ADEs) are overall much more common in ambulatory care, primary care and home (henceforth collectively referred to as community) settings than in hospital settings, it is also important to focus on these hitherto neglected sectors. There is, however, very limited research on the frequency of medication errors and error-related ADEs in Saudi Arabia's (SA's) community settings.

Aims: To estimate the incidence and prevalence of medication errors and associated ADEs in community settings, and to identify the risk factors for these outcomes, with an emphasis on those that are potentially modifiable.

Methods: I have undertaken a phased programme of work. In Phase 1, I undertook a systematic review of the existing research on the epidemiology of medication errors and error-related ADEs, and their risk factors in community settings. Phase 2 was a feasibility study to identify the ambulatory settings and electronic database, evaluate the feasibility of data extraction and data collection from electronic health records (EHRs) and to check the availability and assess the reliability of key outcome measures. Phase 3 was a pilot, retrospective cohort study using clinically important errors in medicine management that were extracted from EHRs. This third phase also focused on assessing the sample size calculations for undertaking a larger cohort study. A random sample of 200 records was selected; a list of all patients who visited the Family Medicine department two weeks before data collection was generated. Each record was given a code number and EHRs were selected using a random number table that was generated using the 'simple random sample without replacement' function in STATA. The final study, Phase 4 was a larger retrospective cohort study to estimate the period prevalence of clinically important errors in medicine management, identify risk factors associated with patients at risk of clinically important errors in medicine management and to compare the estimates from this SA-based study with QRESEARCH analysis of secular trends in the United Kingdom (UK). A random sample of 2000 records was selected using a similar process to Phase 3. All research participants were adults aged

≥18 years. Phases 2-4 were based on the methods used by Avery et al. (2012). Phases 3 and 4 were undertaken in randomly selected samples of 200 and 2000 patients, respectively. Statistical analyses in Phases 3 and 4 were undertaken using STATA (version 14) statistical software.

Results: For Phase 1, I identified a total of 15,302 potentially eligible studies, of which 60 met the inclusion criteria: 53 studies focused on medication errors, three on error-related adverse events and four on risk factors only. None of these studies was undertaken in SA. The prevalence of prescribing errors was reported in 46 studies with prevalence estimates ranging widely from 2.0-94.0%. Inappropriate prescribing was the most common type of error reported.

Only one study reported the prevalence of monitoring errors, finding that incomplete therapeutic/safety laboratory-test monitoring occurred in 73.0% of patients. The incidence of preventable ADEs was estimated as 15/1000 person-years, the prevalence of drug-drug interaction (DDI)-related adverse drug reactions (ADR) as 7.0% and the prevalence of preventable ADE as 0.4%. A number of patients, healthcare professionals and medication-related risk factors were identified, including the number of medications used by the patient, increased patient age (≥75 years), the number of multi-morbidities, the use of anticoagulants, cases where more than one physician was involved in patients' care and care being provided by family physicians/general practitioners (GP).

For Phase 2, I selected the EHRs of King Faisal Specialist Hospital & Research Centre (KFSH&RC) Family Medicine and Polyclinics, Riyadh, SA and the findings confirmed that the pilot study was feasible and likely to yield random samples. More specifically, all information needed for the outcome measures were available in one electronic system and were useable in Phases 3 and 4.

In Phase 3, a random sample of 200 records was selected. The overall period prevalence of patients with at least one medication error over 15 months was 10.0% (95% confidence interval (CI) 5.8 to 14.2). The overall period prevalence of medication errors over 15 months was 16.0% (95% CI 8.2 to 23.8). Risk factors that significantly predicted the overall patients at risk of medication errors were patient's age of ≥65 years and using over-the-counter (OTC) medications.

In Phase 4, a random sample of 2000 records was selected using a similar process to Phase 3. The overall period prevalence of patients with at least one medication error over 15 months was 5.85% (95% CI 4.8 to 6.9). The overall period prevalence of medication errors over 15 months was 8.1% (95% CI 6.5 to 9.7). The overall period prevalence estimate of the first 12 clinically important errors in medicine management in the cohort study was more compared to the QRESEARCH analysis of secular trends. This may reflect the different types of healthcare services provided and the different methods of data extraction between both countries. Risk factors that significantly predicted the overall patients at risk of errors were patient's age of ≥65 years, male gender, Saudi nationality and taking five or more concurrent drugs (polypharmacy).

In both Phases 3 and 4, the highest risk of prescribing errors was found to be for 'Outcome 2a: patients with asthma who had been prescribed a β-blocker'. For monitoring errors, the highest risk was in 'Outcome 7: patients receiving lithium for at least three months who had not received a recorded check of their lithium concentrations in the previous three months'.

Conclusions: This is the first study to investigate medication errors in community settings in SA. This research has revealed that clinically important medication errors are common with a period prevalence estimate of 8.1% and are seen both in relation to the prescribing and monitoring of drugs. Future research should replicate this work in different community contexts in SA and other countries, in order to investigate in greater depth the error-related adverse events and develop and evaluate interventions to decrease clinically important errors in medicine management.

Lay summary

Medication errors are mistakes made during the patient's treatment stages, starting from the time the doctor chooses and writes the prescribed drug until the drug is dispensed by the pharmacist to the patient. In addition, patients/or their caregivers sometimes, make mistakes in the medication they brought themselves. Patient's treatment stage is complex. Mistakes can happen at any stage along this complex pathway. Sometimes patients can be harmed by these mistakes. When a medication error leads to harm, it is called a preventable adverse drug event (ADE). ADEs have been identified as one of the most common causes of preventable error-related harm in hospital care. It is important to also study the safety of the drugs consumed outside the hospital because more medications are very frequently used outside of hospitals and with less supervision compared to inside the hospital.

In Saudi Arabia (SA), only a limited number of research studies on medication errors have been conducted outside of hospital settings, i.e. in the community. I, therefore, aimed to estimate how common are medication errors and preventable ADEs that occur in community settings in SA and understand their risk factors.

I undertook a phased programme of work. In Phase 1, I reviewed the literature on existing research on the rates of occurrence of medication errors and preventable ADEs, and the factors that increase the chance of developing those errors in community settings. The literature review also helped me to identify studies that could serve as a template for my fieldwork in SA. After reviewing this body of literature, I selected and used a list of 21 pre-defined clinically important medication errors in the following research phases based on the methods used by Avery and colleagues (2012). Phase 2 involved a study to choose the ambulatory settings and electronic database and to measure the ability to successfully complete the next two phases of work. Phase 3 was a pilot or small scale study using the list of predefined medication errors. Information from electronic health records (EHRs) was extracted, in order to focus on assessing the sample size calculations for undertaking a larger cohort study. Finally, Phase 4 was a larger cohort study to look at the rate of occurrence of medication errors in a community setting.

The literature review revealed a very wide variation in the medication errors and error-related adverse events rates that were reported in studies; this variation may have been due to the

different populations studied, the different study designs and different outcomes. This review identified important limitations in these studies, as well as gaps in the literature on this topic. For Phase 2, I selected the outpatient clinic in King Faisal Specialist Hospital & Research Centre (KFSH&RC), Riyadh, SA and found that it was feasible to extract and collect the research data from that source. I was able to frame the method of sampling and I was able to successfully complete the next two phases. A pilot study conducted in Phase 3 showed that the prevalence rate was 10% or in other words, a total of 10 outpatients in 100 patients may experience at least one medication error during the study period. A patient's age ≥65 years and using medication the patients brought for themselves increased the chances of medication errors. Therefore, I continued to Phase 4, cohort study, which showed that the prevalence rate was 6% meaning on average 6 outpatients in 100 patients experienced at least one medication error during the study period. A patient's age of ≥65 years, male patients, Saudi nationality and using five or more drugs were all factors identified to increase the chance of patients experiencing a medication error.

In conclusion, this is the first study looking at medication errors in community settings in SA. This study shows that clinically important medication errors are common in SA. These findings now need to be built on with a focus on developing and evaluating interventions to reduce the frequency of these medication errors.

Declaration

I declare that the content and composition of this report are my work unless otherwise stated.

Ghadah Assiri

March 2019

Dedication

To my parents, my husband, Mayar, Bader and my family.

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Abbreviations

ACE	Angiotensin-converting enzyme (inhibitor)
ACOVE	Assessing Care Of Vulnerable Elders
ADE	Adverse drug event
ADI	Adverse drug interaction
ADR	Adverse drug reaction
β-blocker	Beta-blocker
BMJ	British Medical Journal
CASP	Critical Appraisal Skills Program
CDSI	Central Department of Statistics & Information
CHD	Coronary heart disease
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COPD	Chronic obstructive pulmonary disease
CPOE	Computerised provider order entry
DDI	Drug-drug interaction
ED	Emergency department
eGFR	estimated Glomerular Filtration Rate
EHR	Electronic health record
eSiHi	electronic System for Integrated Health Information
EMRO	Eastern Mediterranean Regional Office of the World Health Organization
FDA	Food and Drug Administration
GBD	Global Burden of Disease
GDP	Gross Domestic Product
GI bleed	Gastrointestinal bleeding
GP	General practitioner
HEDIS	Health Plan Employer Data and Information Set
HIMSS	Healthcare Information and Management Systems Society
HIT	Heparin induced thrombocytopenia
ICD	International Classification of Diseases
ICD-10	International Statistical Classification of Diseases and

	Related Health Problems 10th Revision
ICIS	Integrated Clinical Information System
ICPS	International Classifications for Patient Safety
ICU	Intensive care unit
IDU	Inappropriate drug use
INR	International Normalised Ratio
IOM	Institute Of Medicine (now National Academy of Medicine)
IQR	Interquartile range
IP	Inappropriate prescribing
IPET	Improved Prescribing in the Elderly Tool
JBI	Joanna Briggs Institute
KFSH&RC	King Faisal Specialist Hospital & Research Centre
KSU	King Saud University
MDAPE	Medication discrepancy adverse patient events
MOH	Ministry Of Health
NCC-MERP	National Coordinating Council for Medication Error Reporting and Prevention
NGHA	National Guard Health Affairs
NIHR	National Institute for Health Research
NOAC	New Oral Anti-Coagulant
NSAID	Non-Steroidal Anti-Inflammatory Drug
OPEC	Organization of the Petroleum Exporting Countries
OR	Odds ratio
OTC	Over-the-counter (medications)
PBUH	Peace Be Upon Him
PHC	Primary healthcare
PIM	Potentially inappropriate medicine
PINCER	Pharmacist-led information technology-based intervention to reduce rates of clinically important errors in primary care
PPI	Proton pump inhibitor
PPO	Potential prescribing omission
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT	Randomised controlled trial
REC	Research ethics committee
RECORD	REporting of studies Conducted using Observational Routinely-collected health Data Statement
SA	Saudi Arabia
SFDA	Saudi Food and Drug Authority
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool of Older Person's Prescription
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
TB	Tuberculosis
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
YLD	Years lived with disability

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Chapter One: Medication Errors and Adverse Drug Events

1.1 Introduction

The 1990 Harvard Medical Practice (Study II) identified medication as the most common source of injury resulting from medical care.(1) The subsequent report from the Institute Of Medicine (IOM; now named as the National Academy of Medicine), titled "*To Err Is Human: Building a Safer Health System"* brought considerable national and international attention to the problem of errors in hospitals in 2000.(2) In the report, the authors estimated that in the United States of America (USA) some 44,000-98,000 deaths per year were caused by medical errors.(2) Of those deaths, approximately 7,000 were believed to be the result of medication errors occurring either in or outside of hospital.(2) The World Health Organization (WHO) has subsequently identified medication errors as one of the key areas on which to focus attention in order to enhance the safety of ambulatory, primary care, and home settings.(3)

In this chapter, I will introduce the concepts of: a) medication errors, b) error-related adverse drug events (ADEs) or preventable ADEs, and c) adverse drug reactions (ADRs). The definitions of these terms are summarised in Table 1-1. Medication error is the inadvertent inappropriate use of a drug that may or may not result in harm,(4) while ADEs have been defined by Bates et al. (1990) as an "*injury resulting from medical intervention related to a drug*".(5) The majority of ADEs are predictable and dose dependent while a smaller number of ADEs are unpredictable and idiosyncratic or an allergic reaction to a drug; in other words ADRs.(6) ADR or non-preventable reaction "*is an injury due to a medication where there is no error in the medication process*".(7) My focus is confined to medication errors and error-related ADEs or preventable ADEs since as ADRs occur with the appropriate use of a drug they are not due to, or the result of, an error. Table 1-1 below lists the detailed definitions of ADE, ADR, and medication error.

Medication errors and error-related ADEs are common and are responsible for considerable patient harm.(8) In 2007 in the USA, an estimated one medication error per hospitalised patient occurred daily(9) and 1.5 million preventable ADE occurred annually.(9) More specifically, ADEs can lead to morbidity, hospitalisation, increased healthcare costs and, in some cases, death.(8, 10) The cost of drug-related morbidity and mortality has been estimated to be $177.4 billion annually in the USA alone.(11) Since the release of "*To Err Is Human:*

Building a Safer Health System" by the IOM,(2) which focused on acute care settings, most patient safety research has been conducted in hospital settings.(12, 13) International and national policy drivers are however for patients to be increasingly managed in ambulatory, primary care and home settings, in order to realise the goals of more accessible, patient-centred and efficient healthcare.(14) In addition, given that the shift from health worker management to self-management, most medications are now consumed outside of hospital settings, with the patients or a family member in charge of medications administration. Therefore, a more substantial understanding of error occurrence in community care contexts needs to be developed.(13)

	Definition
Adverse drug event (ADE)	"*Injury resulting from medical intervention related to a drug*"(5) As defined by the WHO, an ADE is an event that is "*noxious and unintended and occurs at doses used in man for prophylaxis, diagnosis, therapy, or modification of physiologic functions*". Note that this definition does not include mistakes in prescribing, providing, or administering drugs unless injury results.(15)
	Preventable ADE: 1- "*Is harm caused by the use of a drug as a result of an error. Medication related harm due to error"* National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP).(16) 2- "*Is an injury that is the result of an error at any stage in the medication use—for example, a coma due to an overdose of a sedative"*(7)
	Non-preventable ADE: 1- "*Is drug-induced harm occurring with appropriate use of medication. Medication related harm not due to error "*(NCC-MERP).(16) 2- "*Is an injury due to a medication where there is no error in the medication process—for example, an allergic reaction in a patient not previously known to be allergic to the medication. These are also known as adverse drug reactions, or non-preventable reactions due to side effects or allergic reactions*"(7) 3- **Adverse drug reaction (ADR)** "*Response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function*". (WHO, 2002)
Medication error	*"Any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control*

	Definition
	of the health care professional, patient, or consumer. Such events may be related to professional practice, health-care products, procedures, and systems, including prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use". (NCC-MERP)(17)

Table 1-1. Definitions of adverse drug event, adverse drug reaction and medication error.

1.2 Relationship between medication errors and adverse drug events

Not all medication errors harm the patient. Studies have found that only between 1-10% of medication errors contribute to patient harm.(2, 6, 18, 19) Figure 1-1 shows the relationship between medication errors and ADEs.

If an ADE results from an error, it is described as a 'preventable ADE'; if an ADE does not result from an error, it is referred to as a 'non-preventable ADE'.(7)

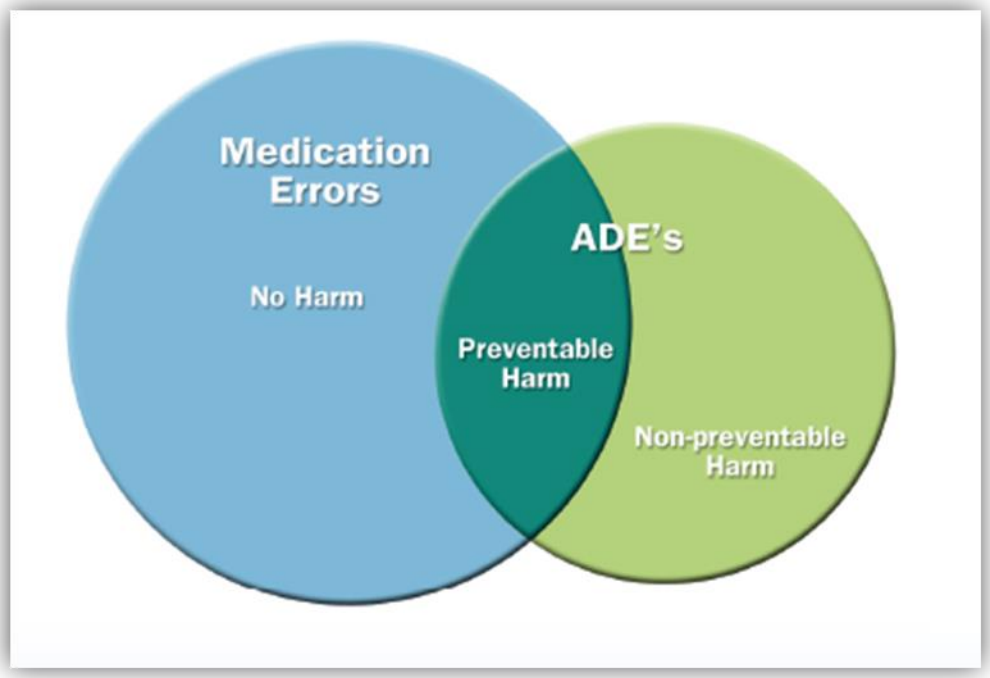

Figure 1-1. Relationship between medication errors and adverse drug events.(7)

1.3 Medication error types

Medication errors can occur at any point in the medicines' management process i.e. during prescribing, transcription, dispensing, administering and monitoring.(7, 20) Medication errors also occur when transferring patients between care settings.(9)

A series of studies has identified that medication errors can occur in the following settings:

- Hospital [Bates et al. (1995) and Kaushal et al. (2001)](6, 21)
- Outpatient [Gandhi et al. (2000)](22)
- Ambulatory and primary care [Gandhi et al. (2003)](23)
- Nursing and home care [Field et al. (2001)](24)
- Transition of care from hospital to home [Martin (2012)](25)
- After discharge [Forster (2005) and Kripalani (2012)](26, 27)
- Home or community dwelling [Sorensen et al. (2006) and Walsh (2008)].(10, 28)

My research focus is on ambulatory, primary care and home sites (henceforth collectively referred to as community) settings.

1.4 Medication error causes

James Reason proposed the "Swiss Cheese Model" of system accidents. This model explains how human and/or organisational structures can potentially prevent, or cause, medication errors. According to this model, a series of barriers are in place to prevent errors from causing harm to humans. However, each barrier has its unintended and random weaknesses, or holes, just like Swiss cheese.(29)

In a landmark systems analysis of ADEs by Leape et al. (1995)(30) the following factors were identified as proximal causes of medication errors: "*lack of knowledge of the drug, lack of information about the patient, rule violations, slip and memory lapses, transcription errors, faulty drug identity checking, faulty interaction with other services, faulty dose checking, infusion pump and parenteral delivery problem, inadequate monitoring, drug stocking and delivery problems, preparation errors, and lack of standardization*",(30) which occur across multiple stages. The term proximal cause is defined as "*the apparent reason the error was made*". A single proximal cause can result in a variety of types of errors. Conversely, one type of error can result from several different proximal causes.

Figure 1-2**Figure 1-2** below is a model offered by Avery et al. (2002),(20) of why and how adverse events occur in primary care. The model, as a whole, shows that different types of system failure can result in an adverse event.

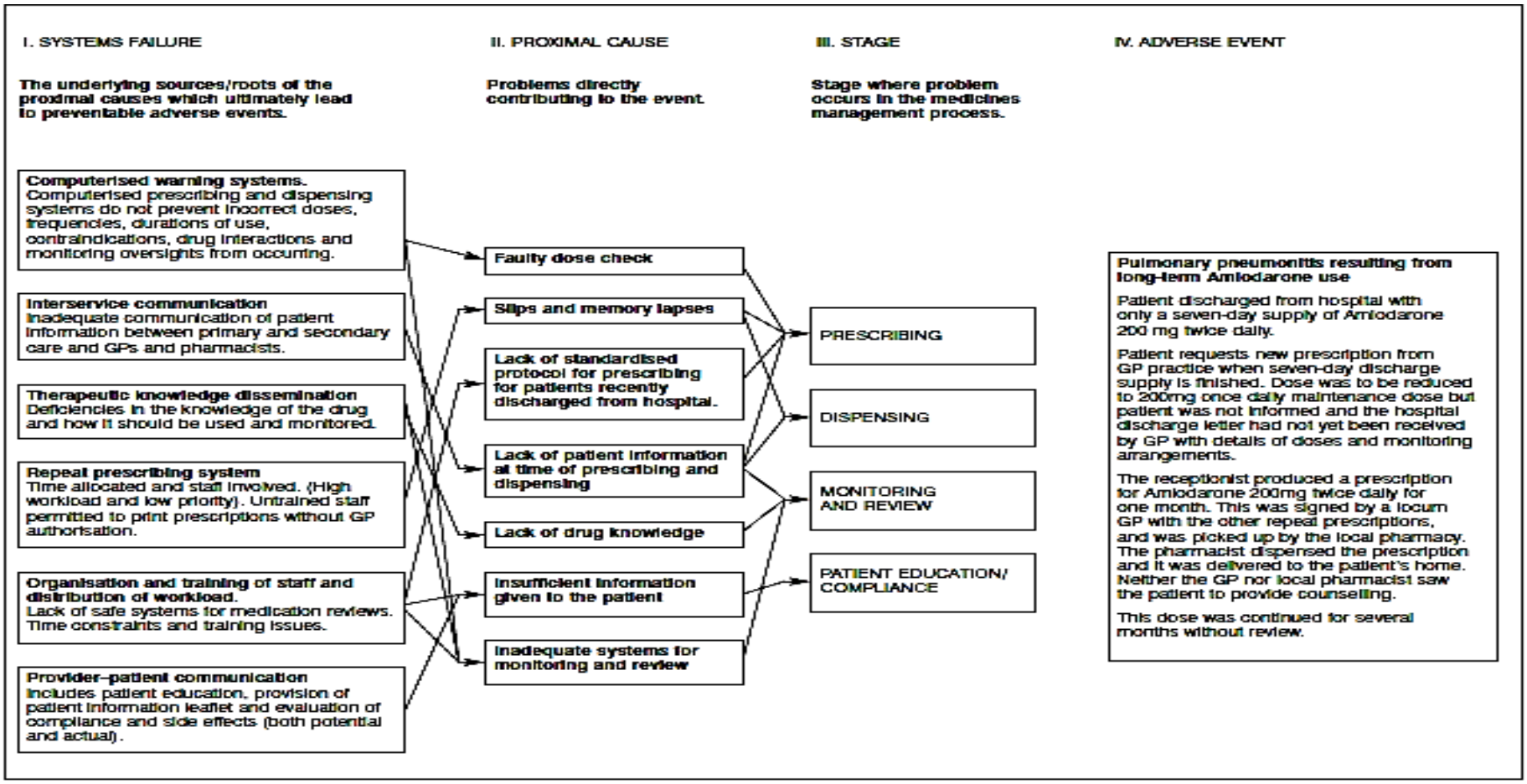

Figure 1-2. A schematic model for understanding the causation of adverse events in primary care.(20)

1.5 Medication error risk factors and outcomes

The different risk factors that increase the risk of medication error occurrence include the following: lack of knowledge, age, polypharmacy (which can be defined as five or more concurrent drugs)(31) or using multiple medications, cognitive status, using high alert medication which are *"drugs that bear a heightened risk of causing significant patient harm when used in error"*(32) or medication with narrow therapeutic index, the latter being *"drugs with small differences between therapeutic and toxic doses*".(33)

The outcomes of medication errors are several, including patient harm, which may manifest as patient discomfort, side-effects, and a temporary or permanent decline in health status, increase in emergency department (ED) attendance, outpatient clinic visit, hospital admissions and death.(2, 7, 34) Children and adults who suffer from multiple long-term conditions with associated complex drug regimens are particularly at risk.(35-37)

1.6 Chapter summary

Many patients are inadvertently and unintentionally harmed by the medical care they receive. Medication errors are a particularly common cause of iatrogenic harm. These errors can occur at any stage of the medicines' management process. The majority of research conducted in this area has been undertaken in hospitals in European, North American, and Australian contexts with a smaller number of studies in community settings and fewer still in the Middle Eastern region.

The available evidence suggests that most of these medication errors are preventable. Understanding the underlying causes of such errors can help in both error prevention and improving medication management processes.

The following chapter will give a brief overview of the Saudi healthcare system, as well as some wider context to the country.

Chapter Two: Saudi Arabia: a Country Profile

2.1 Introduction

The original work in this PhD was undertaken in Riyadh, the capital and largest city of Saudi Arabia (SA). In order to contextualise this work, I will in this chapter provide an overview of both the healthcare system of SA and the medical services available in the ambulatory setting. To achieve this goal, it is also important to consider aspects of SA culture and religious traditions that shape the nature of SA; particularly because SA, within the Arabian Peninsula in the Middle East is the birthplace of Islam.

This chapter provides an insight into SA's population, history, and economy and highlights how Islam shapes notions of health and the healthcare system. Aspects of the Saudi healthcare system that may have a bearing on medication safety will be explained in this chapter. These include the care provided by Saudi physicians to non-Saudi patients and by non-Saudi physicians to Saudi patients,(38) unrestricted access through community pharmacies to medications that are, in many other countries, not available over-the-counter (OTC),(39) and the problem of buying prescribed medication as non-prescribed medication in the community settings.(40) Considering these aspects during my data collection can help facilitate an understanding of patient practice and the risks of medication errors.

SA is undertaking a major redevelopment of its healthcare system, moving from a primarily hospital-based system to a more integrated care system with a strong primary care-based health system. After the Alma-Ata Declaration, a ministerial decree was issued to establish Primary Healthcare (PHC) centres. The move to the PHC system resulted in an increase in the number of PHC centres and the improvement of free care provided, including preventive and curative services.(41) In recent years, SA has been progressively developing its PHC system to increase the availability and accessibility of its health services to the entire population.

Given the dearth of global studies looking at medication error in the community, and the global and particular shift in SA from secondary and tertiary care to community-based care, the focus of my work is important and timely. I plan to do the first in-depth work looking at medication errors in Riyadh, the capital and largest city in SA.(41)

2.2 Geography

SA is the largest nation in the Middle East, with a land area of about 2,250,000 square kilometres consisting mostly of desert. It shares a border with Iraq, Jordan, and Kuwait to the north, the Sultanate of Oman and Yemen to the south, the Bahrain, Persian Gulf, Qatar and the United Arab Emirates to the east and Gulf of Aqaba and the Red Sea to the west (see Figure 2-1).

Figure 2-1. Map of SA.(42)

2.3 History

Prophet Mohammad peace be upon him (PBUH), who is believed by Muslims to be the Messenger of Allah (God), was born in Makkah, which is in the west of SA. His main objective was to call upon people to believe in monotheism and spread the message of Islam.

Prophet Muhammad PBUH moved to the city of Madinah in 571 CE, where later the Hejri (lunar) Calendar was developed. Islam's most sacred scripture is the Holy Qur'an (which the Prophet received from Allah) and Sunnah (the traditions and saying of Prophet Mohammed PBUH).

The history of the region was dominated by the rise and spread of the Ottoman Empire from the 13th Century onwards with increasing coalescing of different power bases occupying territories in the area including Najd, Hejaz, Hassa, Assir areas and North Yemen. In 1745, Prince Muhammad bin Saud from the Najd and Sheikh Muhammad Ibn Abdul Wahab launched a religious movement calling for the purification of Islam by spreading the original message of Allah and Prophet Mohammed PBUH.

With the flair-up of World War I, the British found neighbourhood partners in the Hijazi Hashemites and the Al Saud family, both eager to assert their freedom from the Ottomans; thereby aiming to ensure Arab independence.(43)

After World War I, the Arabian Peninsula divided into two empires: Hashemite Emara of Makkah which related to Governor of Makkah Sharif, Husayn Ben Ali; and the Najd area.(43)

The history of SA, in its current form as a state, began with its foundation in 1932 by King Abdulaziz Al Saud. After his death in 1953, his son King Saud succeeded him to the throne. With the rise of a new global economy requiring an energy source for expansion, the oil rich lands of SA provided the nation with not only economic prosperity, but also a great deal of political leverage in the international community. Despite the abundant oil wealth, extravagant spending ultimately led to governmental deficits and foreign borrowing in the 1950s.(43) Since then, SA has initiated major reforms in education and health, as well as in science and technology related research. In January 2015, Salman bin Abdulaziz Al Saud (Prime Minister of SA and Custodian of the Two Holy Mosques) was crowned the seventh king of SA.

2.4 Population

As of 2018, SA's population according to the Central Department of Statistics & Information (CDSI) of the Kingdom is 33,413,660 people with a total average life expectancy of 74.8 years: 73.5 years for males and 76.1 years for females. Non-Saudi residents make up 37.8% of the total population.(44)

Age/Gender	Male	Female	Total
Young (< 15 years old)	4,186,398	4,034,482	8,220,880
Adult (15-64 years old)	14,486,665	9,630,263	24,116,928
Elderly (≥ 65 years old)	567,893	507,959	1,075,852
Total	19,240,956	14,172,704	33,413,660

Table 2-1. Population estimates in SA, 2018.(44)

2.5 Economy

SA's economy is oil based, with the nation holding 18% of the world's petroleum reserves.(45) Since the discovery of oil in the 1930's, SA has gone through a major and rapid transition from an agricultural subsistence land to a major economic power. SA is an important member of the Organization of the Petroleum Exporting Countries (OPEC).(45) The Saudi economy depends mainly on oil demand and is shaped by external pricing.(46) The oil and gas sectors account for about 50% of Gross Domestic Product (GDP), and about 70% of export earnings.(45) The service sector accounts for 43% of the economy, while agriculture accounts for 5% of the economy.(47) The proven crude oil and natural gas reserves according to OPEC are 266,260 million barrels and 8,715 billion cubic metres, respectively.(45) The total expenditure on health was 4.7% of GDP, which equates to $2,466 per person in 2014.(48)

Understanding the global battle on oil and the reasons for the price reductions are beyond the scope of this PhD. However, recognising the impact that the shifting price will have on the national budget and consequently on the budget allocated for healthcare is important.

Apart from petroleum, the Kingdom's other natural resources include iron, gold, silver and copper. The national currency is the Saudi Riyal.(45)

The rapidly growing Saudi populations, in addition to providing free services for all Saudi nationals, have been key factors in the rise of health expenditures in SA.(49)

Table 2-2 shows the employment and unemployment rates in SA, reported by the CDSI.

Indicators on Saudi human resources (2017)	Overall rate (%)	Male	Female
Employment rate (15 years and above)	93.9	96.6	79.0
Unemployment rate (15 years and above)	6.1	3.4	21.0
Saudi employment rate (15 years and above)	87.1	92.4	69.1

Table 2-2. Statistical data and indicators on Saudi human resources for 2018 (first quarter).(50)

2.6 Health profile

2.6.1 Disease burden

According to the most recent data available, the leading causes of death in SA in 2016 were ischemic heart disease, road injury, cerebrovascular disease, chronic kidney diseases, lower respiratory tract infections, Alzheimer's disease, diabetes mellitus, congenital defects, liver cancer and falls.(51) Table 2-3 shows the leading 10 causes of years lived with disability (YLD) in SA.(52)

1	2	3	4	5	6	7	8	9	10
Low back and neck pain (0.8)	Migraine (1.2)	Major depressive disorder (1.0)	Anxiety disorders (1.1)	Neck pain (0.9)	Diabetes mellitus (1.1)	Other musculoskeletal disorders (1.4)	Iron-deficiency anaemia (3.0)	Age-related and other hearing loss (0.6)	Opioids use disorder (1.95)

Table 2-3. Leading 10 causes of years lived with disability (YLD) with ratio of observed YLD to YLD expected on the basis of Socio-demographic Index in SA, 2016.(52)

2.6.2 Health services

SA provides the following health services: in-patient, emergency, outpatient care and primary care which include maternal and neonatal, haemodialysis and organ transplant, medical rehabilitation, medical commissions, mental health, nutrition, forensic medicine, dental services, ophthalmology, dedicated health services during pilgrimage (Hajj) season and home healthcare.(53, 54) Table 2-4 below shows developments in the healthcare services of SA over the last 90 years.

Year	Evolution of services	Number
1926	Establishment of a Health Directorate in Jeddah and the opening of Ajyad Hospital in Mecca and Bab Shareef Hospital in Jeddah	-
1927	The Directorate was renamed the Directorate of General Health and Ambulances	-
1951	The Directorate became the Ministry of Health (MOH)	11 hospitals and 25 dispensaries
1966 - 1976	40-fold increase in oil revenues led to much greater capital investment in healthcare infrastructure	-
1970	First 5-year National Development Plan was instituted by the Saudi government to promote development in a number of areas, including healthcare system(47) Increase in number of hospitals	74 hospitals and 9,039 beds
1978	According to the Alma-Ata Declaration, the Saudi MOH decided to activate and develop the preventive health services by adopting the PHC approach(41)	-
1980	A ministerial decree was issued to establish PHC centres(41) Establish suitable premises for primary care throughout the country(41)	-
1985-1987	Real expansion of healthcare system begins	65 new hospitals and 312 new PHCs were established

Year	Evolution of services	Number
1990	Increase in private health sector	-
2002	Increase in number of hospitals	331 hospitals and 47,242 beds
2009	82% of client visits to PHC centres MOH facilities (41)	408 hospitals providing 55,932 beds

Table 2-4. The history and evolution of healthcare services in SA.(41, 47, 55)

2.6.3 Health and Islam

At this point in this background chapter on SA, it is important to consider religious issues and their impact on health. Islam is the national religion in SA, which as stated above, is based on the Holy Qur'an and Sunnah. Muslims believe that health, illness, and death all come from Allah. Though Islamic belief indicates that those who are unwell should seek medical advice, the belief that illnesses originate from Allah may lead some patients not to seek healthcare. Jabir ibn Abdullah (a prominent companion of Prophet Muhammad PBUH) reported Allah's Messenger Prophet Mohammad PBUH as saying: "*There is a remedy for every malady, and when the remedy is applied to the disease it is cured with the permission of Allah, the Exalted and Glorious*".(56)

The Islamic faith encourages regular exercise, moderate eating and drinking, no alcohol, personal cleanliness and other constructive practices that promote health and well-being such as meditation, fasting, and breastfeeding.(57) For example, as regards diet, Allah said in The Holy Qur'an "*O children of Adam, take your adornment at every* Mosque, *and eat and drink, but be not excessive. Indeed, He likes not those who commit excess*". (Al-A'raf 31)

The Prophet Mohammad PBUH encouraged asceticism in life and eating and drinking without excess as he said: "*No man fills a container worse than his stomach. A few morsels that keep his back upright are sufficient for him. If he has to, then he should keep one-third for food, one-third for drink and one-third for his breathing*".(58)

Muslins should fast in the month of Ramadan and are encouraged to fast on Monday and Thursday. Pork and alcohol are prohibited according to Islam. Islam discourages the use of any substances that may harm or change the body or disrupt the mind.

Even though exercise is not mentioned directly in the Holy Qur'an, Muslims are encouraged to follow Prophet Mohammad's lifestyle and they will be rewarded for following him. Walking to the Mosque, starting the day early, the movement involved in the daily performance of prayer, the performance of Hajj and visiting Makkah (Umrah) are acts of the Prophet PBUH, which require physical effort and are considered good for health.

Physical activities such as swimming, archery and horse riding were advocated by the Prophet Mohammad PBUH as being of value. He said, "*Any action without the remembrance of Allah is either a diversion or heedlessness excepting four acts: Walking from target to target [during archery practice], training a horse, playing with one's family, and learning to swim*".

Although Islam advocates for moderation in diet, 28.7% of Saudi's population (aged 15 years or older) have obesity resulting in the main from negative health-related behaviours.(59) Several factors are attributed to the increase in the incidence of obesity in SA. These factors include increasing sedentary lifestyles in both children and adults. In children, behaviours such as low levels of physical activity, spending large amounts of time watching television, sleeping for less than seven hours have all been found to be associated with obesity.(60) Saudi women have limited physical activity due, in part, to their dependence on house-maids. Food intake together with the pattern of diet have been identified as major reasons for obesity, including skipping breakfast, and the frequent use of soft drinks,(60) a high daily per capita energy supply and fat intake (during the period 1971-2005) was estimated to be present in 60% of SA's population.(60)

Within the Qur'anic tradition particular attention to care of the body, especially cleanliness is emphasised. The Qur'an advocates washing all the exposed areas of the body before prayer, hands, feet, face, mouth, nostrils, etc., five times a day (ablution). Allah said in The Holy Qur'an "*O you who have believed, when you rise to [perform] prayer, wash your faces and your forearms to the elbows and wipe over your heads and wash your feet to the ankles*". (Al-Ma'idah 6)

This supportive health activity is now emphasised globally in healthcare to prevent the spread of disease; in particular, hand washing and personal hygiene, are a core part of Islamic life. The Prophet Muhammad PBUH stressed brushing teeth as part of a Muslim's daily routine. There is therefore value in understanding the way in which the health routines of those living in SA are shaped by Islamic beliefs and also value in understanding whether such

articulations of beliefs will be able to shed light on strategies to reduce medication errors, on self-management and on decision making in community settings.

Islam and pilgrimage

SA has a unique position in the Islamic world, as the nation contains the two holiest cities of Islam: Mecca and Medina. In the pilgrimage (Hajj) season, about two million pilgrims from all over the world perform the Hajj annually, which is a major challenge that requires planned and organised efforts to ensure adequate healthcare services are available.(41) Free medical services are provided during the Hajj.

Islam and healthcare

Islam has shaped the structural healthcare system in SA in several ways. Hospitals in SA have separate wards for men and women, a female nurse is assigned for the care of women when female patients are examined by a male physician, especially in the areas of obstetrics and gynaecology care.(61) If gender-specific care is impossible, a male nurse caring for women should always be joined by either a female staff member or one of the patient's adult relatives. Islam allows for Muslim healthcare professionals to manage or care.(57) If the patients can fast during Ramadan, healthcare providers can adjust the time of medication administration after breaking their fast. Drug products that contain alcohol or pork are not allowed to be given to Muslim patients.

In hospitals, prayer areas and rest rooms should be available for the performing of personal ablutions; and the sound of the prayer should be heard inside and around hospitals.(61)

2.7 Healthcare system

Until the end of the 1970s, the health services in SA were predominantly curative focusing on treatment of existing health diseases. Then after the Alma-Ata Declaration 1978, a ministerial decree was issued to establish PHC centres, with an agreement to achieve 'health for all by the year 2000' as shown in Table 2-4**Table 2-4**.(38, 41) Establishment of a PHC strategy and applying a referral system has helped to reduce the number of visits to outpatient clinics.(41)

The most up-to-date rating of SA's healthcare system according to the WHO was in the year 2000, when it was rated at 26th of 190 health systems globally.(62)

Healthcare is provided free to all Saudi citizens by the MOH, which "*is responsible for the country's health system. It has a well-defined, decentralized organisational and administrative structure. Its functions include: strategic planning, formulating specific health policies, supervising all health service delivery programs, as well as monitoring and controlling all other health related activities*".(63) The MOH serves as a national health service for the Saudi population.(46)

Foreign non-Saudi workers who represent 80.5% of the whole non-Saudi population according to the CDSI of the Kingdom in the first quarter of 2018,(50) can use the MOH facilities only in an emergency.(46) The majority of foreign workers and their dependents receive healthcare through employment-based or self-paid insurance.(55) Health insurance is provided through The Council of Cooperative Health Insurance, which was established in 1999. This insurance facility is applicable to Saudis and non-Saudis in the private sector where their employers pay the health costs.(41)

2.7.1 Pharmaceutical services

Until 2007, the MOH was the primary pharmaceutical regulatory authority in SA. In 2007, via Royal Decree, the Saudi Food and Drug Authority (SFDA) took over the function of MOH. Established in 2003, the SFDA is responsible for developing and enforcing a regulatory system for the pharmaceutical sector.(64)

Each hospital has pharmaceutical services with community pharmacies, which stock a full range of medicines included in the MOH Drug Formulary.(65) The governmental central medical stores are responsible for distribution of pharmaceuticals to the public and private sectors hospitals.(64)

In all governmental health services, all Saudis can receive medicines free of charge.(64) Non-Saudis are eligible for services and medications through their insurance policy.(64, 66)

According to one report, about 48.8% prescription medications were dispensed without a prescription.(40) In April 2018, the MOH warned against selling antibiotics without prescriptions and stated "*violators will face legal actions which include a fine of up to 100 thousand riyals, abolition of the license and imprisonment for up to six months*".(67) In SA, a number of prescription medications are also available as OTC; the exceptions being narcotics, psychotropic substances and antibiotics. The Food and Drug Administration (FDA) defines

OTC dr*ugs as "drugs that have been found to be safe and appropriate for use without the supervision of a health care professional such as a physician, and they can be purchased by consumers without a prescription*".(68)

Currently in SA, there are nine public and private pharmacy schools. The first College of Pharmacy was established in King Saud University (KSU), Riyadh, in 1959. The pharmacy education in SA is a five year programme, for a Bachelor of Pharmacy degree.(69)

2.7.2 Delivery of health services in Saudi Arabia

Health services in SA are delivered and provided by three main sectors:(41)

1. The government sector, the MOH, is the owner and provider of healthcare services, which account for over 62% of all inpatient care.
2. Other governmental sector healthcare providers, which deliver primary, secondary, and tertiary care and which are funded outside the budget of the MOH include:
    - Armed Forces Hospital
    - King Faisal Specialist Hospital & Research Centre (KFSH&RC), Riyadh
    - KFSH&RC, Jeddah
    - Ministry of Education (school health units)
    - Ministry of Higher Education (University Hospitals)
    - Ministry of Interior Medical Services
    - National Guards Medical Services
    - Red Crescent Society
    - Royal Commission Hospitals in Jubail and Yanbu
    - University Hospitals and Medical Centres in the Kingdom.
3. The private sector: provides all level of healthcare services and charges a fee.

The government's and other governmental sector healthcare providers have a decentralised healthcare delivery system.(70) The MOH is responsible for advising other government agencies and the private sector on ways to achieve the government's health objectives.(63)

Table 2-5 summarises the health resources in SA offered by the three healthcare sectors.

The total number of physicians in 2016 was 75,740, increasing to 82,375 physician in 2017.(71)

	Health resources at the MOH	**Health resources within other governmental sectors**	**Health resources in the private sector**
A-Health facilities			
Target population	Saudi nationals: Free health services to all Saudi nationals with no restrictions. Non-Saudis: Eligibility is restricted to legal residents who are under individual affiliations.	Employees and their families and dependents of the different governmental body **The Ministry of Higher Education (University hospitals)**: A- Saudis: all are eligible B-non-Saudis: Eligibility is restricted to legal residents who are under individual affiliations. **The Ministry of Education:** government school children **Red Crescent:** emergency services	All
Finance	By the MOH	By the Ministry of Finance through their respective ministries and agencies.	By personal ownership or companies.
Health services	Primary, secondary, and tertiary care through healthcare centres, hospitals, medical & dental	Primary, secondary and tertiary care through healthcare centres, hospitals, medical & dental services, and	Primary, secondary and tertiary care. Different private practices have different degree of comprehensiveness of

	Health resources at the MOH	Health resources within other governmental sectors	Health resources in the private sector
	services, and medication	medication **University hospitals**: medical education and training programmes, and they also conduct health research in collaboration with other research centres	health services according to the size of the practice.
B- Dispensaries and pharmacies (total number)			
Pharmacies			8,114 private pharmacies, representing a rate of one pharmacy per 3,912 individuals(54)
C- Health manpower (total number: Saudi and non-Saudi)(71)			
Physicians	42,609	16,346	23,420
Dentists	3,996	1,283	10,420
Nurses	103,990	35,808	45,895
Pharmacists	3,853	2,304	22,155
Allied health professionals	59,646	30,214	22,001

Table 2-5. Health resources in SA by the three healthcare providers: Ministry Of Health, other governmental agencies and the private sector.(54, 70, 71)

2.7.3 Structure of healthcare levels in Saudi Arabia

The MOH supplies and provides its public healthcare services at three levels: primary, secondary, and tertiary. In SA, there are 20 health regions, each led by a Regional Director General of Health Services who is directly responsible to the Deputy Minister of Health for Executive Affairs. The directorate is responsible for staff supervision and evaluation, recruitment and welfare, and training.(63)

A. Primary healthcare (PHC) centres

Primary care provides both preventive and curative healthcare services. Primary care involves "*basic health services for all members of the community, and represents the first level of community contact with the health services*".(72)

In recent years, SA has been progressively developing the primary care system to increase availability and accessibility of its health services to the entire population.(41)

Data from a nationally representative multistage survey on healthcare utilisation of individuals aged 15 years or older, shows that most Saudi nationals do not use the PHC centres for general health examination despite their free cost and local availability.(73)

Male and female healthcare providers are available in the PHC centres; the patient has the right to decide on having a male or female medical professional, and the waiting areas are separated between male and female patients.(74)

The PHC centres emphasise an eight element approach to health: "*educating the population concerning prevailing health problems and the methods of preventing and controlling them, provision of adequate supply of safe water and basic sanitation, promotion of food supply and proper nutrition, provision of comprehensive maternal and child healthcare, immunization of children against major communicable diseases, prevention and control of locally endemic diseases, appropriate treatment of common diseases and injuries, and provision of essential drugs*".(41)

The number of the healthcare centres in the 20 regions that provide PHC from the MOH in SA was 2,259 centres in 2013,(53) which increased to 2,325 centres in 2016.(54)

For the referral system between different levels of care, the PHCs are linked to general hospitals, which, in turn, are linked to tertiary care in all MOH facilities. Primary care physicians fill in a predesigned standardised referral form with the relevant clinical and social information. Services in secondary care require a referral from a PHC, except in emergency cases.(75, 76) Patients can access secondary care directly through an ED. Services in tertiary care need a referral from PHC, except in emergency cases.(75) Patients cannot access tertiary care directly.

The services provided by PHC centres are: *"Maternal health, child health, immunization, management of chronic disease (e.g. hypertension and diabetes), dental health, provision of essential drugs, environmental health (e.g. water and sanitation), food hygiene, health education, disease control"*.(63)

B. Secondary healthcare (General hospitals)

General hospitals accept patients who need additional advanced care via a process of referral from the PHC centre. In 2016, there were 470 general hospitals in SA with 70,844 beds.(54) Cases including cardiovascular diseases, obesity, diabetes, hypertension, and asthma and chronic obstructive pulmonary disease (COPD) are referred to these secondary healthcare facilities. Services include "*Obstetrics and gynaecology, medical, surgical, paediatric, dental, emergency service. Some are affiliated to medical college for undergraduate and postgraduate clinical training. Antenatal care is provided at the primary care health centres with two referrals to the secondary care hospital, at 16-18 weeks for ultrasound scan and at 34-36 weeks for a final check-up*".(63)

C. Tertiary healthcare (Specialised hospitals)

The government provides and finances tertiary care services. Cases that need more complex levels of care are transferred to the tertiary central or specialised hospitals (e.g. KFSH&RC and King Khalid Eye Specialist Hospital).(41) Examples of cases referred to the specialised hospitals include pituitary tumours and congenital malformations.

2.7.4 Health information system

The variation in healthcare systems and providers in SA has led to differences in the ways the healthcare facilities are provided, including differences in the information system used across the healthcare system. As a result, patient information/records have become distributed in

different healthcare facilities without a provider having the patients' complete information/record except in rare cases where the patient chooses to receive healthcare from one provider at all times. As a consequence, patients may be given different medications which may affect patient safety.(77)

According to the Country Cooperation Strategy for WHO and SA 2012-2016, the health information system is described as following:

"The Ministry of Health is promoting the use of information technology in order to improve the quality of data and evolve towards paperless management. Hospital facilities are using International Classification of Diseases, Tenth Revision (ICD-10) in order to code causes of morbidity and mortality. The only long established medical scientific research centre is located at the KFSH&RC, which receives its budget from the government".(46)

Use of the electronic health record (EHR) system is gradually moving into MOH facilities, which were not previously connected to each other or to other private organisations.(41) The KFSH&RC and the National Guard Health Affairs (NGHA) have implemented the EHRs and electronic information.(41, 77)

2.7.5 Access and barriers to health services in Saudi Arabia

A recent systematic review aimed at providing an overview of the quality of PHC centres and identifying barriers to access quality healthcare in SA identified that there were good levels of access to immunisation (83-94%), maternal care (67-95%), and screening and treatment of epidemic diseases, while the access was lower than the targets for health education, chronic illnesses e.g. hypertension, and low referral rates for diagnostic purposes and specialised care (38) Another study showed that: "*in order to improve access to services, 90% of primary care centres established appointment systems, registers, and follow-up systems*".(47)

Furthermore, there is a shortage of services for some groups of patients such as the elderly, adolescents, and individuals with special needs.(41) Large sections of the population, especially those living in remote areas, do not have the ability to easily access healthcare facilities.(41)

Physicians have noted that it is difficult to understand some patients due to low levels of education in the community and lack of a common language with which to communicate.(38)

An estimated 40% of patients experience language barriers; a problem directly related to the high number of non-Saudi national primary care professionals serving at the PHC level who do not have Arabic or English as their first language.(38)

2.7.6 Medication safety in Saudi Arabia

Given the increasing importance of patient safety, it is important to focus on the issues of medication safety and medication errors. Medication safety is still a new concept in SA that was first initiated by the SFDA. However, some MOH hospitals and other sectors have started implementing the concept.(78) Some studies were conducted in SA focusing on medication errors, (79-83) mainly in hospital settings. It was found that only 30% of hospitals in SA had a medication committee, and only 9% had a medication safety officer.(81)

In a study done in 2010, 65 different healthcare professionals were divided into nine groups to join round-table discussions. The objective was to explore their perspectives on medication safety in hospitals and community settings in SA and to improve medication safety practice.(39) The study addressed the factors related to medication safety problems; unrestricted public access to medications from various hospitals and community pharmacies, communication gaps between healthcare institutions, limited use of important technologies such as computerised provider order entry (CPOE), and the lack of medication safety programmes in hospitals.(39)

2.8 Chapter summary

Until oil was discovered, SA was a poor country with limited resources, an underdeveloped infrastructure, and subsistence agrarian living for many members of its more rural population. Its healthcare system has been only relatively recently developed and much investment is currently taking place to improve the system's quality standards and increase the availability of services. SA is going through a rapid transition to increase the reach and quality of its PHC services and to refocus continuity of care from hospital to primary health settings.

Improving healthcare has been challenging due to the need to provide high quality healthcare for the rapidly growing population at an affordable cost, the need to improve the implementation of electronic health record systems, and the majority of health workers are foreigners. This latter point, together with the large number of non-Saudi residents in the country frequently gives rise to difficulties in ensuring effective communication between

health providers and their patients. In view of the recent healthcare reforms in SA involving the building up of primary care services, my thesis focuses on the issue of medication safety in the community and primary care context. There is an urgent need to understand more about medication safety in SA especially, at the primary care level.

The following chapter will present the aims and objectives of my PhD and provide an overview of the methods employed.

Chapter Three: Aims, Objectives, and Overview of Methods

3.1 Introduction

There is limited understanding of the frequency of medication errors and error-related ADEs in community settings in SA. This chapter details the aims and objectives of my PhD and provides an overview of the methodology and methods that were used to gather and analyse data. This PhD involved undertaking a four phased programme of work: Phase 1 was a systematic review; Phase 2 was a feasibility study; Phase 3 was a pilot retrospective cohort study; and Phase 4 was a retrospective cohort study.

It should be noted that Phase 1 of this research focused on both medication errors and error-related ADEs, but Phases 2, 3 and 4 focused solely on medication errors.

3.2 Aims

The main aims of the research were to investigate the epidemiology of medication errors and error-related ADEs. More specifically, I sought to:

1. Estimate the incidence and prevalence of medication error and associated ADEs in community (i.e. ambulatory, primary care and home) settings
2. Identify risk factors for medication errors and error-related ADEs with an emphasis on those that were potentially modifiable.

3.3 Objectives

The specific objectives of the overall PhD are detailed below:

In Phase 1, I sought to:

1. Estimate the incidence/prevalence of medication errors in community settings
2. Estimate the incidence/prevalence of error-related ADEs in community settings
3. Identify risk factors associated with medication errors and error-related ADEs.

In Phase 2, in the context of Riyadh, SA, I sought to:

1. To identify the ambulatory setting and electronic database
2. To evaluate the feasibility of data extraction and data collection from EHRs
3. To check the availability and assess the reliability of key primary, secondary, composite secondary and revised updated outcome measures
4. To inform plans for the pilot retrospective cohort study (Phase 3).

In Phase 3, in the context of Riyadh, SA, I sought to:

1. Pilot the study procedures
2. Inform sample size calculations for undertaking the larger retrospective cohort study
3. Inform plans for undertaking a definitive large retrospective cohort study
4. Estimate the period prevalence of clinically important errors in medicine management
5. Identify risk factors associated with patients at risk of clinically important errors in medicine management.

In Phase 4, in the context of Riyadh, SA, I sought to:

1. Estimate the period prevalence of clinically important errors in medicine management
2. Identify risk factors associated with patients at risk of clinically important errors in medicine management
3. Compare the QRESEARCH analysis of secular trends in the United Kingdom (UK) with the estimates I obtained in SA.(84)

3.4 Overview of methods

My research was conceptualised as a phased programme of work (Figure 3-1). Phase 1, involved undertaking a systematic review of the existing research and evidence on the epidemiology of medication errors and error-related ADEs in community settings. Phase 2 was a feasibility study. Phase 3 was a pilot retrospective cohort study using clinically important errors in medicine management and extracting data from EHRs, which was undertaken in KFSH&RC, Riyadh. The focus was on assessing the feasibility of, and informing sample size calculations for, undertaking a larger cohort study. Finally, Phase 4

was a larger retrospective cohort study undertaken in adults (≥ 18 years old) based on a study by Avery et al. (2012).(85)

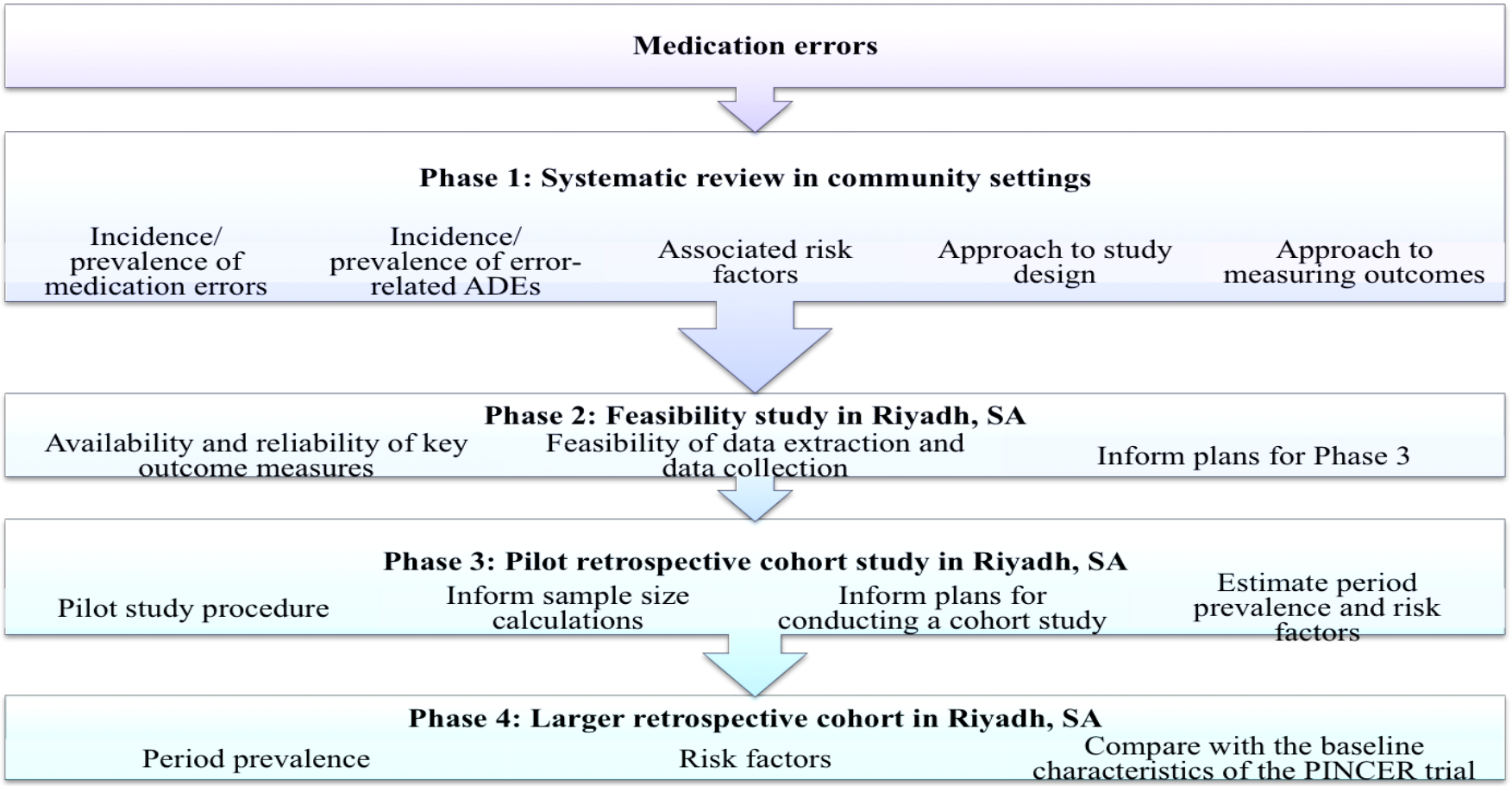

Figure 3-1. PhD phased programme overview.

Chapter Four: Phase 1: Investigating the Epidemiology of Medication Errors and Error-related Adverse Drug Events in Adults in Primary Care, Ambulatory Care and Home Settings: a Systematic Review

4.1 Introduction

In order to determine the epidemiology of medication errors and error-related ADEs and risk factors in the community settings, I had undertaken Phase 1, a systematic review of the literature. The rationale was to identify, select and critically appraise all relevant evidence in order to gather existing knowledge, understanding, and update on the previous studies done. Systematic review method will give an unbiased and replicable representation of current knowledge with reference to my topic compared to the literature review, which is mainly descriptive, and have a source of selection bias. Prior to undertaking further primary work in this area, it is important to take stock of the current evidence base, reflect on the quality of the evidence, distil key findings that have the potential to provide both estimates on the frequency of medication errors and error-related ADEs, and understand the factors underpinning this important source of preventable harm. The aim of this systematic review was to investigate the epidemiology of medication errors, error-related adverse events as well as risk factors for errors in adults managed in community care contexts (i.e. primary care, ambulatory care and home settings. It should be noted that this phase focused on both medication errors and error-related ADEs, but Phases 2, 3 and 4 focused solely on medication errors.

The study protocol was developed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and was registered in PROSPERO.(86, 87) The detailed systematic review protocol has also been published and detailed in Appendix 3.(88) There follows the full paper of this systematic review.

4.2 Systematic review full paper

BMJ Open

What is the epidemiology of medication errors, error-related adverse events and risk factors for errors in adults managed in community care contexts? A systematic review of the international literature

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ABSTRACT

Objective To investigate the epidemiology of medication errors and error-related adverse events in adults in primary care, ambulatory care and patients' homes.

Design Systematic review.

Data source Six international databases were searched for publications between 1 January 2006 and 31 December 2015.

Data extraction and analysis Two researchers independently extracted data from eligible studies and assessed the quality of these using established instruments. Synthesis of data was informed by an appreciation of the medicines' management process and the conceptual framework from the International Classification for Patient Safety.

Results 60 studies met the inclusion criteria, of which 53 studies focused on medication errors, 3 on error-related adverse events and 4 on risk factors only. The prevalence of prescribing errors was reported in 46 studies: prevalence estimates ranged widely from 2% to 94%. Inappropriate prescribing was the most common type of error reported. Only one study reported the prevalence of monitoring errors, finding that incomplete therapeutic/safety laboratory-test monitoring occurred in 73% of patients. The incidence of preventable adverse drug events (ADEs) was estimated as 15/1000 person-years, the prevalence of drug–drug interaction-related adverse drug reactions as 7% and the prevalence of preventable ADE as 0.4%. A number of patient, healthcare professional and medication-related risk factors were identified, including the number of medications used by the patient, increased patient age, the number of comorbidities, use of anticoagulants, cases where more than one physician was involved in patients' care and care being provided by family physicians/general practitioners.

Conclusion A very wide variation in the medication error and error-related adverse events rates is reported in the studies, this reflecting heterogeneity in the populations studied, study designs employed and outcomes evaluated. This review has identified important limitations and discrepancies in the methodologies used and gaps in the literature on the epidemiology and outcomes of medication errors in community settings.

Strengths and limitations of this study

- This is the first systematic review on the epidemiology of medication errors and medication-associated harm in community settings. The use of the International Classification for Patient Safety conceptual framework helped with framing and organising the findings from this systematic review.
- A rigorous and transparent process has been employed, which included no language restrictions in undertaking searches, independent screening of titles, abstracts and full-text papers, independent data extraction, and critical appraisal of included studies by two reviewers.
- Outcomes have been reported in a variety of ways using different tools and methodology, which made it difficult to undertake any quantitative pooled summary of the results.
- Despite the comprehensiveness of the searches, we found no data regarding errors during medication dispensing and administration. This might be due to the lack of 'dispensing error' and 'administration error' terms in our search strategy, although 'medication therapy management' was included as a more overarching search term.
- There is at present no agreed, consistently applied set of confounders that should be taken into account when trying to make causal inferences.

INTRODUCTION

Patient safety is a public concern in healthcare systems across the world.[1] Medication errors and error-related adverse drug events (ADEs) are common and are responsible for considerable patient harm.[1] More specifically,

Box 1 Key definitions

- Adverse drug event (ADE): Bates *et al*[84] define ADE as *'an injury resulting from medical intervention related to a drug'*.[84] Some ADEs are caused by underlying medication errors and therefore they are preventable.
- Medication error: The National Coordinating Council for Medication Error Reporting and Prevention defines a medication error as *'any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use'*.[85] Medication errors can result from any step of the medication-use process: selection and procurement, storage, ordering and transcribing, preparing and dispensing, administration, or monitoring.[1]
- Non-prescription drugs: Medicines that can be sold legally without a drug prescription.
- Over-the-counter (OTC) drug: The Food and Drug Administration defines OTC *drugs as 'drugs that have been found to be safe and appropriate for use without the supervision of a health care professional such as a physician, and they can be purchased by consumers without a prescription'*.[86]
- Prescription drug: Drugs that cannot be sold legally without a prescription.

ADEs can lead to morbidity, hospitalisation, increased healthcare costs and, in some cases, death.[1] It has been estimated that 5%–6% of all hospitalisations are drug-related,[2 3] with one estimate suggesting that ADEs causing hospital admission in the UK occur in around 10% of inpatients; approximately half of these ADEs are believed to be preventable.[4] The cost of medication errors worldwide has been estimated as US$42 billion/year.[5]

Since the release of *To Err is Human: Building a Safer Health System* by the Institute of Medicine (now the National Academy of Medicine),[6] which focused on acute care settings, most patient safety research has been conducted in hospital settings.[7 8] Given that international and national policy drivers are for patients to be increasingly managed in primary, ambulatory and home settings in order to realise the goals of more accessible, patient-centred and efficient healthcare,[9] there is an increased sense of urgency to further focus attention on community care contexts, particularly in relation to medication safety. With an ageing population, particularly in economically developed countries, as well as the use of polypharmacy, there is a need to empower patients, particularly those with chronic diseases, to self-care safely.

The aim of this systematic review was to investigate the epidemiology of medication errors, error-related adverse events and risk factors for errors in adults managed in community care contexts (ie, primary care, ambulatory and home settings). Box 1 provides definitions of the key terms employed in this review.

METHODS

Protocol and reporting

The study protocol was developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and was registered in PROSPERO.[10 11] The detailed systematic review protocol has also been published.[12]

Eligibility criteria/study selection

Studies conducted in adults (≥18 years) who were looked after in the community and living in their own or family homes without home healthcare or nursing home were eligible for inclusion in this review. The studied patients could have been self-managing, receiving care in primary care or ambulatory care settings, or any combination of the above. Studies were included if they were population-based, cross-sectional or cohort studies, which were suitable to estimate the incidence and prevalence of medication errors or ADEs. These study designs and case–control studies were considered eligible to study risk factors for the development of error-related ADEs. Studies with prescribed and/or over-the-counter (OTC) medications as the exposure of interest were eligible.

Paediatric studies (<18 years) and studies on patients receiving care in hospital at home settings (ie, continuous medical and/or nursing care provided to patients in their own homes), in nursing homes, as hospitalised inpatients or in emergency departments (ED) were excluded. Randomised controlled trials were excluded since these could not be used to reliably assess the incidence and/or prevalence of the outcomes of interest. Existing reviews were also excluded since the focus was on the primary literature. Incompletely reported studies, for example, in the form of abstracts, were not eligible for inclusion. Studies on illegal substance abuse, herbal products and those focusing on particular medications were also excluded.

No restriction on the language of publication was employed.

Data sources and search strategy

Search terms were developed based on the systematic review protocol.[12] The search terms and detailed search strategies are presented in online supplementary appendix 1. In summary, these involved identifying search terms (and their synonyms) in relation to medication safety, community care settings and study design, and combining these concepts with the Boolean operator AND to identify studies that intersected all three search concepts of interest. Examples of the search terms used included the following: for the outcome: medication safety, medication error, preventable adverse drug event and patient error; for the setting: ambulatory care, outpatient, self-care, primary healthcare and general practice; and for the study design: cohort study, cross sectional study and observational study. Six biomedical databases were searched, including the Cumulative Index to Nursing

and Allied Health Literature, EMBASE, Eastern Mediterranean Regional Office of the WHO, MEDLINE, PsycINFO and Web of Science, between 1 January 2006 and 31 December 2015. Google Scholar was searched for additional studies. An international panel of experts was also contacted to identify unpublished work and research in progress (online supplementary appendix 1). The reference list of all included studies was further reviewed for additional possible eligible studies.

The databases were searched by GAA. The title and abstracts were then independently screened for eligible studies according to the above detailed selection criteria by GAA and a second reviewer, NAS. The corresponding authors of the eligible articles were contacted if additional information was needed. Disagreements were resolved by discussion between the reviewers or by arbitration by a third reviewer, AS, if a decision could not be reached. Full-text articles were retrieved from selected studies and reviewed according to the selection criteria. Each copy of the selected studies was retrieved and the reason for excluding other studies was clearly noted.

Data extraction and risk of bias assessment

Data were independently extracted and recorded onto a customised data extraction sheet by two reviewers (GAA and NAS, or GAA and MAM). Discrepancies were resolved by discussion or by arbitration by an additional reviewer (AS), if necessary.

Key information, such as study design, study type (retrospective, prospective), population of interest, exposure of interest, outcomes of interest and main findings, was extracted.

The risk of bias assessment was independently carried out on each study by two reviewers (GAA and NAS, or GAA and NA) using the Critical Appraisal Skills Programme (CASP) quality assessment tool for cohort and case–control studies,[13] and cross-sectional studies were assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for descriptive studies.[14] Any disagreements were resolved by consensus or by arbitration by a third reviewer (AS) if a decision could not be reached. Each study was given an overall grading as being at high, medium or low risk of bias.

Data synthesis

Data were summarised in detailed data tables, which included information on the incidence, prevalence, relative risk and ORs, together with 95% CIs, for each study (where available). A descriptive and narrative synthesis of the extracted data was undertaken.

The following is the definition of incidence rate used in this review: *'the number of patients with one or more [medication error or preventable ADE] (numerator) divided by the total number of patients at risk per time unit (denominator)'*.[15] The following is the definition of prevalence rate used in the data extraction: *'the number of patients experiencing one or more [medication error or preventable ADE] (numerator) divided by the total number of patients in the study population (denominator)'*.[16] The prevalence rate per population was either reported and extracted directly from the included study or calculated from data provided in the study.

Box 2 Classification of definitions used in this systematic review

- Administration error: 'Any discrepancy between how the medication is given to the patient and the administration directions from the physician or hospital guidelines'.[1]
- Prescribing error: 'Medication error occurring during the prescription of a medicine that is about writing the drug order or taking the therapeutic decision, appreciated by any non-intentional deviation from standard reference such as: the actual scientific knowledge, the appropriate practices usually recognized, the summary of the characteristics of the medicine product, or the mentions according to the regulations. A prescribing error notably can concern: the choice of the drug (according to the indications, the contraindications, the known allergies and patient characteristics, interactions whatever nature it is with the existing therapeutics, and the other factors), dose, concentration, drug regimen, pharmaceutical form, route of administration, duration of treatment, and instructions of use; but also the failure to prescribe a drug needed to treat an already diagnosed pathology, or to prevent the adverse effects of other drugs'.[17]
- Inappropriate prescribing: 'The use of medicines that introduce a significant risk of an adverse drug-related event where there is evidence for an equally or more effective but lower-risk alternative therapy available for treating the same condition. Inappropriate prescribing also includes the use of medicines at a higher frequency and for longer than clinically indicated, the use of multiple medicines that have recognized drug–drug interactions and drug–disease interactions, and importantly, the under-use of beneficial medicines that are clinically indicated but not prescribed for ageist or irrational reasons'.[87]
- Monitoring error: 'Failure to review a prescribed regimen for appropriateness and detection of problems, or failure to use appropriate clinical or laboratory data for adequate assessment of patient response to prescribed theory'.[17]
- Dispensing error: 'Deviation from the prescriber's order, made by staff in the pharmacy when distributing medications to nursing units or to patients in an ambulatory pharmacy setting'.[17]
- Other discrepancies:'Any differences between the medication described by the patient and caregivers with the drugs listed by their general practitioners (GP) or between the medications listed in the discharge letter for the primary care physician with those in the patient discharge medication list'.[31 32]

We worked with the definitions of medication errors and error-related ADEs employed in individual studies. These errors may have occurred anywhere in the medicines' management process.[1] Medication errors were described according to (1) the stage in the medicines' management process when the error occurred, that is, prescribing, dispensing, administration and monitoring[1]; and (2) the type of error that occurred in each stage according to the conceptual framework for the International Classification for Patient Safety (ICPS) definitions (box 2).[17]

Risk factors were categorised as patient, healthcare professional and medication-related risk factors.

Changes from the original protocol

The following changes were made from the plans described in the research protocol[12]: (1) due to the large quantity of studies found during the initial search and because of medications and practice changes over the years, only studies published in the last 10 years were included: 1 January 2006–31 December 2015; (2) only studies with the incidence or prevalence rate per number of patients were included; and (3) meta-analysis was not possible due to the heterogeneity of outcomes, methods and definitions.

RESULTS

A total of 13 033 potentially eligible studies were identified after removing duplicates, of which 59 studies met the inclusion criteria. One additional study was identified through hand-searching. Therefore, a total

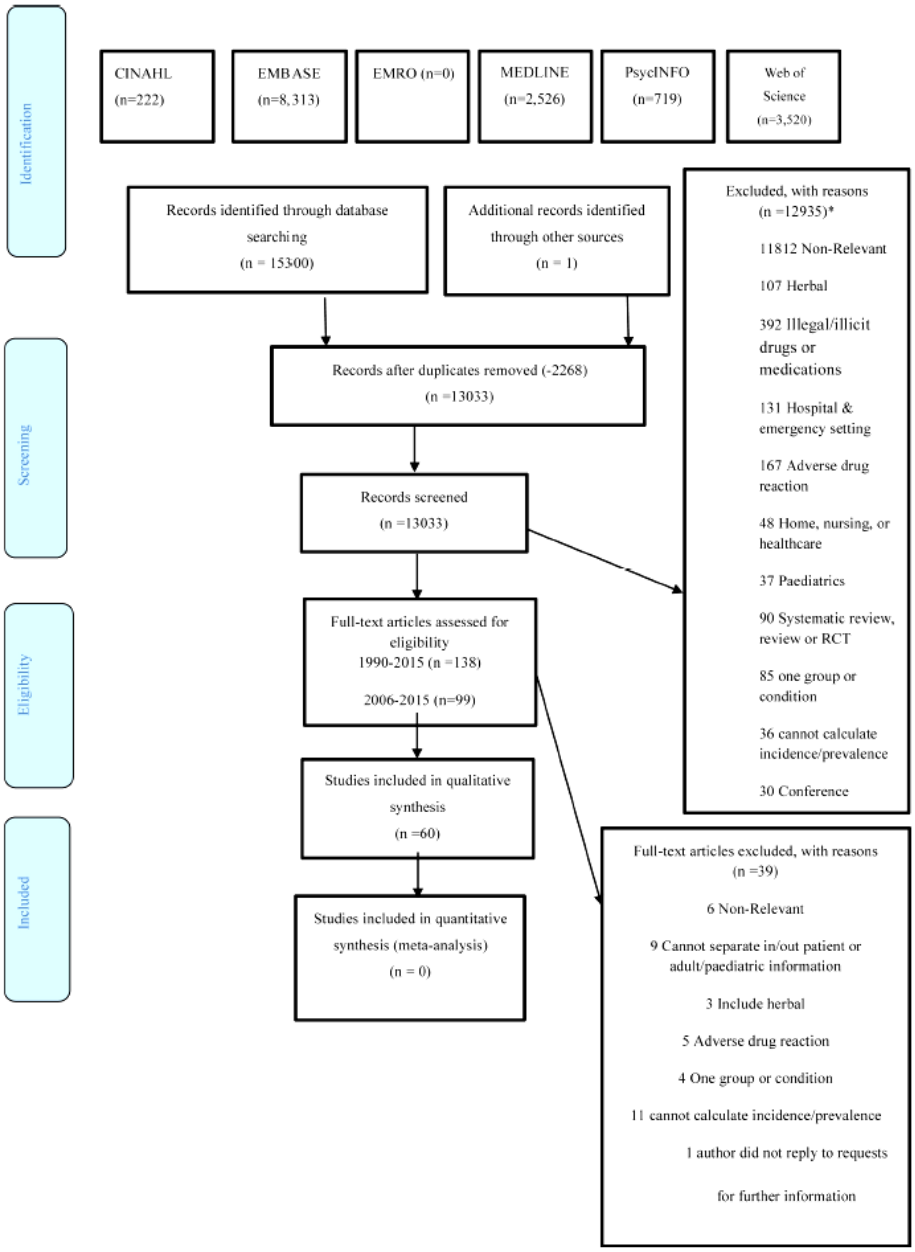

Figure 1 PRISMA flow diagram (from Moher *et al*[88]). CINAHL, Cumulative Index to Nursing and Allied Health Literature; EMRO, Eastern Mediterranean Regional Office; RCT, randomised controlled trial. *Articles may be duplicated between the excluded groups.

of 60 studies were included in the systematic review (figure 1).

One study was available only in German and one in Spanish. Those two papers were retrieved and translated into English by native speakers.[18 19]

The key characteristics of all included studies are presented in table 1. The quality assessments of these studies are summarised in tables 2A and 2B.

Nine studies were conducted in Asia, 4 in Australia, 32 in Europe, 8 in North America, 5 in South America and 2 were conducted across continents (one study covering two Australian countries, three European countries, one North American country and one South American country,[20] and one study across two Australian countries, four European countries, one North American country and one South American country).[21] Nineteen studies were conducted in primary healthcare or general practice contexts, 15 studies in home or community settings, 16 studies in ambulatory care or outpatient settings, 5 studies in community pharmacies and 2 studies in post-discharge settings, while 3 studies used secondary data analysis.

Eleven studies enrolled adults in all age groups (>18 years), three studies reported the mean age only,[22–24] one enrolled those 55 years or older,[25] five enrolled those aged 60 years or older,[26–30] and the majority of studies (n=40 studies, 67%) enrolled patients 65 years or older. If the study included adult and paediatric data, only relevant adult data were extracted.

The quality of the cross-sectional or descriptive studies using the JBI Critical Appraisal Checklist was high for nine studies, moderate for ten studies and low for one study. The quality of the cohort studies using the CASP quality assessment tool was high for 37 studies and moderate for 3 studies.

Different methods of medication errors and error-related adverse events identification were used in the studies, including data review (electronic/paper-based medical record review, lab review, prescription review), database analysis, patient survey (face-to-face or telephone interview and survey or questionnaire), patient self-report and home visits.

MEDICATION ERRORS

Incidence and/or prevalence

We found no study reporting data on the incidence of medication errors. Estimates of community setting medication error prevalence were available from 53 studies.[18–21 23 24 26 27 29–73]

Self-reported medication errors

The period prevalence of self-reported medication errors was measured in four cross-sectional studies by Adams *et al*, Lu and Roughead, Sears *et al*[21] and Mira *et al*.[20 21 72 73] In the first three studies, the period prevalence was reported as 2%, 6% and 6%, respectively,[20 21 72] while in Mira *et al*'s study 75% of elderly patients with multiple comorbidities and polypharmacy (five or more drugs) reported having made at least one mistake with their medication (including errors related to dose, similar appearance of medications and lack of understanding of the physician's instructions).[73] In this study, in 5% of cases, errors due to drug confusion had very severe consequences, requiring a visit to the emergency services or hospital admission.[73] That wide differences in prevalence were seen between the first three studies and the last may be due to population factors. Mira *et al*'s study population comprised older polymedicated patients with multiple comorbidities. This elderly group had a greater risk of error, while the first three studies had populations including any patient over 18 years.

MEDICATION ERROR ACCORDING TO MEDICINES' MANAGEMENT PROCESS

Prescribing errors

The point or period prevalence of prescribing errors was reported in 46 studies. In these studies, prescribing errors included errors in drug indications, drug–disease interactions, drug–drug interactions (DDI) and dosing error, as well as inappropriate prescribing, which was the most common error reported.

Indication

Koper *et al*[23] found that, on average, 2.7 medications per patient were not indicated, with a total of 94% of patients having medications prescribed by the general practitioner (GP), but not mentioned in the indication of the UpToDate.[23]

Drug–disease interactions or contraindications

Drug–disease interactions were measured in one study by Mand *et al*[33] with a prevalence of 10%.[33]

Drug–drug interactions

The prevalence of DDIs was measured in 11 studies and ranged from 2% to 58%.[23 24 26 27 30 34–39] This could in part have been due to the fact that different DDI screening tools were used, namely DDI compendia and ePocrates RX, Thomson Micromedex program, Pharmavista database, BotPlus program of the General Council of Pharmacists' Official Colleges, British National Formulary 2010, Italian computerised interaction database, DrugDigest, Drugs, Micromedex and Medscape.

Inappropriate prescribing

A. The prevalence of potentially inappropriate medication (PIM) was measured in 37 studies in the elderly age group only (≥65 years) and ranged from 5% to 94%.[18 19 23 26 29 37 40–70] This extremely wide range of inappropriate prescribing prevalence estimates is likely to be, at least in part, due to the different detection tools used, namely Beers 2003, the 2006 Health Plan Employer Data and Information Set, improved prescribing in the elderly tool, Medication Appropriate Index, PRISCUS and Screening Tool of Older

Table 1 Systematic review data extraction table

Key characteristics of included studies

	Author, year	Country/city	Study design/type	Population of interest	Exposure of interest	Outcome of interest	Main finding	Conclusion, n/N (%)	Additional notes
Self-reported medication errors									
1.	Adam *et al*, 2009[72]	Australia	Cross-sectional	Analysis of data from 3522 adults participating in stage 2 of the North West Adelaide Health Study aged ≥18 years	Unclear	Self-reported adverse event (medication, diagnosis and others). Using survey.	Of the total 3522 survey participants, 148 (4.2%) reported an adverse event causing harm in the previous 12 months, giving an annual incidence of 4.2% (95% CI 3.4% to 5.0%). Medication error: The main types of adverse events perceived as causing harm were medication error (reported by 46% of the 148 participants reporting adverse events).	Medication error prevalence: 68/3522=1.9%	Subjective data rather than objective
2.	Lu and Roughead, 2011[80]	Australia, Canada, New Zealand, UK, USA, Germany and The Netherlands	Cross-sectional (secondary analysis)	11 910 adult respondents aged ≥18 years. Data from the 2007 Commonwealth Fund International Health Policy Survey.	Prescribed drug	Self-reported medication error and compare factors associated with medication errors across the seven countries. Using survey.	Self-reported medication errors prevalence: 752 respondents had medication error (Australia=7.4%; Canada=5.7%; New Zealand=5.9%; UK=5.2%; USA=7%; Germany=5.2%; The Netherlands=8%). Risk factors across countries included seeing multiple specialists, multiple chronic conditions, hospitalisation and multiple emergency room visits.	Medication error prevalence: 752/11 910=6.3%	Prevalence for medication error alone from table 1, while the risk factors for both medical and medication error.
3.	Sears *et al*, 2012[21]	Australia, Canada, France, Germany, the Netherlands, New Zealand, UK and USA	Descriptive (secondary/ retrospective analysis)	9944 adults aged ≥18 years from the community setting	Taking medication regularly	Patient-related risk factors associated with self-reported medication errors. Using telephone survey.	Medication error prevalence: 570 respondents with medication errors occurring in the community setting. Approximately 4 out of every 5 self-reported medication errors occurred in the community setting.	Medication error prevalence: 570/9944=5.7%	Risk factors for both hospital and community setting
4.	Mira *et al*, 2013[73]	Alicante, Spain	Cross-sectional	382 elderly aged ≥65 years from primary care. Patients on polypharmacy (five or more drugs) and with comorbidity: cardiovascular (51.6%); diabetes (34.3%).	Prescribed and self-medications	Frequency of mistakes in communication between the physician and the patient and their medication error in the last year. Using semistructured interviews.	Medication error prevalence: 75.1% of the patients reported having made at least one mistake with the medication in the last year. Risk factors: Multiple comorbidities (p=0.006), frequent changes in prescription (p=0.02), not considering the prescriptions of other physicians (p=0.01), inconsistency in the messages (p=0.01), being treated by various different physicians at the same time (p=0.03), a feeling of not being listened to (p<0.001) or loss of trust in the physician (p<0.001). *The error due to drug confusion had very severe consequences, requiring a visit to the emergency service or hospital admission.	Medication error prevalence: 287/382=75%	Consequence*
Risk factors									
5.	Sorensen *et al*, 2006[76]	4 states of Australia	Cross-sectional, prospective	204 general practice patients living in their own home aged 37–99 years	Prescribed drugs	Prevalence and interrelationships of medication-related risk factors for poor patient health outcomes identifiable through 'in-home' visit observations.	Risk factors: Prevalence of nominal medication-related risk factors and health outcomes among the sample of 204 patients. 1. Multiple medication storage locations used=17 (8.3%). 2. Expired medication present=40 (19.6%). 3. Discontinued medication repeats retained=43 (21%). 4. Hoarding of medications=43 (21%). 5. Therapeutic duplication present=50 (24.5%). Administration error: 6. No medication administration routine=56 (27.5%). 7. Poor adherence=107 (52.5%). 8. Confused by generic and trade names=114 (55.9%).		
6.	Vuong and Marriott, 2006[78]	Melbourne, Australia	Descriptive	142 discharged adults aged ≥55 years who were returning to independent care at home. Patients at risk of medication misadventure.	Discharge prescribed drugs	Unnecessary medicine stored at home as a risk factor. Using home visit within 5 days of discharge.	Unnecessary medicine stored at home prevalence: 85/142=60%. 85 (60%) of 142 patients who received a home visit allowed removal of medicines that had expired or no longer required. Prescribing error: drug duplication prevalence: 32 (27%) patients allowed removal of 82 duplicate packs of the same item that was no longer required. A total of 390 medicines were removed with a mean of 4.6 medicines per patient (range 1–21).	Unnecessary medicine stored at home prevalence: 85/142=60%	No information on how many patients had unnecessary medicine. Information available is on the patient allowed to remove unnecessary medicine.
7.	Pit *et al*, 2008[74]	New South Wales, Australia.	Cross-sectional study	849 elderly aged ≥65 years from general practice	Self-medications	Prevalence of self-reported risk factors for medication misadventures. Tool used: Medication Risk Assessment Form (patient survey)	Risk factors: 1. Using at least one medication for more than 6 months (95%). 2. More than one doctor involved in their care (59%). 3. Had three or more health conditions (57%). 4. Used five or more medicines (54%). 5. ADRs, in the last month 39% of participants experienced difficulties sleeping, felt drowsy or dizzy (34%), had a skin rash (28%), leaked urine (27%), had stomach problems (22%) or had been constipated (22%).		*ADR as a risk factor for medication misadventure may not be related to the use of medication in all cases.
8.	Mosher *et al*, 2012[75]	Iowa, USA	Cohort prospective	310 elderly aged ≥65 years who were cognitively intact from a Veterans Administration primary care clinic	Taking five or more non-topical medications	Association of health literacy with medication knowledge, adherence and ADEs. Using interview and chart review.	Total: 310 patients Prevalence of ADEs: ADEs occurred in 51 patients (16.5%) of the patients within the first 3 months of the study, which increased to 119 patients (38.4%) over the full 12-month follow-up period. Risk factor: Association of health literacy with ADEs: The incidence of ADEs at 3 and 12 months appeared higher among patients with low health literacy, but this was not statistically significant.	Low health literacy increased the risk of ADEs.	

Continued

Table 1 Continued

Key characteristics of included studies

	Author, year	Country/city	Study design/type	Population of interest	Exposure of interest	Outcome of interest	Main finding	Conclusion, n/N (%)	Additional notes
Medicines' management process:									
9.	Koper *et al*, 2013[23]	Austria	Descriptive	169 patients from general practice taking five or more medicines. Mean age: 76.4±8.5SD years. Of the 169 patients, 158 were elderly aged ≥65 years.	Prescribed and OTC drug	Medication errors including non-evidence-based medications, dosing errors and potentially dangerous interactions in all patients. Potential interactions were identified using the Lexi-Interact database. PIMs in subgroup of elderly patients according to the PRISCUS list. Using case report form filled by the GPs.	Prescribing error prevalence: Indication: 158 of the 169 patients (93.5%) had at least one non-evidence-based medication. Dosing error: 74 of the 169 patients (43.8%) had at least one dosing error. DDI prevalence: Category D interactions: 99 patients (58%) had at least one category D interaction. Category X interactions: 4 patients (2.4%) had at least one category X interaction. PIM prevalence: 59 of seniors (37.3%) had at least one medication that was inappropriate.	Medication error prevalence: 1. Non-evidence-based medications: 158/169=93.5%. 2. Dosing error: 74/169=43.8%. 3. Category D drug interaction: 99/168=58%; category X drug interaction: 4/168=2.4%. 4. PIMs: 59/158=37.3%.	A medication was classified as non-evidence-based if the indication for use indicated by the GP was not mentioned in any peer-reviewed chapter of UpToDate.
10.	Mand *et al*, 2014[33]	Germany	Descriptive retrospective	24 619 elderly aged ≥65 years from family practice with at least one diagnosis named in the Beers list	Prescribed drug	PDDI frequency and whether there are gender-related or age-related differences. Analysis from electronic patient records.	Prescribing error: Contraindication or drug–disease interaction prevalence: 10.4% of elderly were exposed to at least one PDDI. Risk factors: 1. Patients over 75 years (OR 1.10, CI 1.05 to 1.15). 2. Number of drugs prescribed (>4 drugs: OR 1.91, CI 1.83 to 2.00). 3. Blood clotting disorders/receiving anticoagulant therapy (OR 2.38, CI 2.15 to 2.64) showed the strongest association with PDDI.	PDDI prevalence: 2560/24 619=10.4%	
11.	Gagne *et al*, 2008[16]	Regione Emilia-Romagna, Italy	Cohort retrospective	4 222 165 regional Emilia-Romagna residents. Outpatient aged from 0 to ≥85 years.	Prescribed drug	Clinically important potential DDI. Risk factors. Outpatient prescription data from the Regional Emilia-Romagna. DDI screening tool: a list of clinically important potential DDIs included 12 drug pairs that could be captured using the regional Emilia-Romagna database.	Prescribing error: DDI prevalence: exposed to potential DDI adults (19 to ≥85 years)=7893. Unexposed adult=7013. Total=14906.	DDI prevalence: 7893/14 906=53%	Risk factors for all age groups including paediatrics. All age groups included so results should be considered cautiously.
12.	Dallenbach *et al*, 2007[24]	Geneva, Switzerland	Descriptive, retrospective file review	591 outpatients, mean age 39 years	Prescription drug and drug currently taking	Clinically significant ADI. Prescription review. DDI screening tool: DDI compendia and (ePocrates RX) with clinical decision support.	Prescribing error: DDI prevalence: In 135 of the consultations, a potentially clinically significant ADI was identified.	DDI prevalence: 135/591=23%	
13.	Obreli Neto *et al*, 2011[25]	Brazil	Cross-sectional	2627 elderly aged 60–88 years from the primary healthcare	Prescribed drug	Potential risks in drug prescriptions: DDI and PIM. Using prescription review. DDI screening tool: (Drug Digest, Medscape and Micromedex). PIM using Beers criteria 2003.	Prescribing error: DDI prevalence: Using DrugDigest showed that 4.7% and 28.4% of the elderly presented at least one potential DDI classified as major and moderate, respectively. Using Medscape showed that 3.4% and 19.3% of the elderly presented at least one potential DDI classified as major and moderate, respectively. Using Micromedex showed that 3.1% and 29.1% of the elderly presented at least one potential DDI classified as major and moderate, respectively. Prescribing error: PIM prevalence: 26.9% of the patients had prescriptions with at least one PIM.	DDI prevalence: 3.1%–29.1% PIM prevalence: 26.9%	
14.	Secoli *et al*, 2010[30]	Sao Paulo, Brazil	Cross-sectional	2143 community-dwelling elderly aged ≥60 years. Data were obtained from the SABE (Health, Well-Being and Ageing) survey.	≥2 prescribed drug use	Potential DDIs and identify associated factors. Using home interview. DDI screening tool: Micromedex Healthcare Series.	Prescribing error: DDI prevalence: 568/2143=26.5%. Risk factors: The use of six or more medications (OR 3.37, 95% CI 2.08 to 5.48) or having hypertension (OR 2.56, 95% CI 1.73 to 3.79), diabetes (OR 1.73, 95% CI 1.22 to 2.44) or heart problems (OR 3.36, 95% CI 2.11 to 5.34) significantly increased the risk of potential DDI.	DDI prevalence: 568/2143=26.5%	
15.	Obreli Neto *et al*, 2012[27]	5 cities of Brazil	Cross-sectional	12 343 elderly aged ≥60 years from the primary public health system	Prescription for two or more drugs (prescribed both within and across prescriptions)	Potential DDIs (presence of a minimum of 5 days overlap in supply of an interacting drug pair) and predictor of DDI. Using medical prescriptions and patients' medical records review. DDI screening tool: DDI checker programmes (DrugDigest, Drugs, Micromedex and Medscape).	12 343 patients (5855 exposed; 6488 unexposed). Prescribing error: DDI prevalence: 47.4% Risk factors: Female sex (OR=2.49 (95% CI 2.29 to 2.75)), diagnosis of ≥3 diseases (OR=6.43 (95% CI 3.25 to 12.44)) and diagnosis of hypertension (OR=1.68 (95% CI 1.23 to 2.41)) were associated with potential DDIs. Age was associated with an increasing risk of DDIs. Number of prescribers, number of drugs consumed, ATC codes and drugs that act on CYP450 presented positive associations with potential DDIs in univariate and multivariate analyses of drug therapy characteristics.	DDI prevalence: 5855/12 343=47.4%	

Continued

Table 1 Continued

Key characteristics of included studies

	Author, year	Country/city	Study design/type	Population of interest	Exposure of interest	Outcome of interest	Main finding	Conclusion, n/N (%)	Additional notes
16.	Indermitte *et al*, 2007[34]	Switzerland	Descriptive	434 passer-by customers aged ≥18 years from community pharmacies	Prescription-only medicines and OTC drug	Potential drug interactions. 1. Observation of customer contacts and interviews with passer-by customers purchasing selected OTC drugs. 2. Telephone interviews with regular customers treated with selected prescription-only medicines identified in community pharmacies' databases. DDI screening tool: Pharmavista database.	Prescribing error: DDI prevalence: Observation of passer-by customers. Of 1183 passer-by customers observed, 164 purchased at least one of the selected OTC drugs. 102 (62.2%) of those subjects were interviewed. 43 (42.2%) mentioned taking prescribed drugs and 3 of them were exposed to potential drug interactions of moderate severity. Telephone interview with regular customers. Out of 592 regular customers selected from the community pharmacy database, 434 (73.3%) could be interviewed. Prevalence of DDI in regular customers: 69 (15.9%) of them were exposed to a potential drug interaction between purchased OTC drug for self-medication and their prescription-only medicines. Furthermore, 116 (26.7%) regular customers were exposed to potential drug interactions within their prescribed drugs and in 28 (6.5%) multiple (>2) potential drug interactions were found.	DDI prevalence: 3/102=3%, 69/434=16%, 116/434=26.7%	
17.	Mahmood *et al*, 2007[35]	USA	Cross-sectional, retrospective	2 795 345 patients who filled prescriptions for medications involved potential DDI from 128 Veterans Affairs medical centres. Ambulatory care clinic.	Prescribed drug	Clinically important DDI. Database analysis of pharmacy records. DDI screening tool: a list of 25 potential DDI.	Prescribing error: DDI prevalence: The overall rate of potential DDIs was 21.54 per 1000 veterans exposed to the object or precipitant medications of interest.	DDI prevalence: 2.15%	Age not mentioned
18.	Lapi *et al*, 2009[37]	Dicomano, Italy	Cohort, a two-wave, population-based survey	568 community-dwelling elderly aged ≥65 years	Prescription and non-prescription drugs used at least 1 week before enrolment	Suboptimal prescribing: Inappropriate medication=1991 Beers criteria (13 items out of the original 39 (33.3%) Beers list medications were considered). DDI screening tool: Micromedex Drug-Reax system. Using population-based survey.	Prescribing error: Potential DDI prevalence was significantly higher in 1999 compared with 1995 (30.5% vs 20.1%; p<0.001). Inappropriate prescriptions were significantly higher in 1995 compared with 1999 (9.1% vs 5.1%; p=0.004). 1995 / 1999 / P values Inappropriate medication: 47 (9.1%) / 26 (5.1%) / 0.004 DDI: 97 (20.1%) / 147 (30.5%) / <0.001 Major DDI: 20 (4.7%) / 24 (5.6%) / 0.585 Risk factors: Polypharmacy always predicted a substantial increase in the risk of the PIM and DDI.	Potential DDI prevalence: 30.5%, p<0.001 Inappropriate medication prevalence: 5.1%, p=0.004	
19.	Nobili *et al*, 2009[38]	Lecco, Italy	Cross-sectional, retrospective	58 800 community-dwelling elderly aged ≥65 years registered under the local health authority of Lecco	Receiving at least two coadministered prescriptions	DDIs and associated risk factors (age, sex and number of prescriptions). DDI screening tool: Italian computerised interaction database. Analysed all prescriptions dispensed from 1 January 2003 to 31 December 2003.	Prescribing error: DDI prevalence: 9427 elderly people (16%) were exposed to drug combinations with the potential for 13 932 severe DDIs. Mean number of DDI per patient was 0.2 (range 0–9). Risk factors: Age and number of chronic drugs were associated with an increasing risk of DDIs. The adjusted OR increased from 1.07 (95% CI 1.3 to 1.11) in patients aged 70–74 years to 1.52 (95% CI 1.46 to 1.60) in those aged 85 or older. Elderly taking more than five chronic drugs had a statistically significant higher risk of potentially severe DDIs (OR=5.59, 95% CI 5.39 to 5.80) than those receiving less than 3 (reference category) or 3–5 chronic drugs (OR=2.71, 95% CI 2.63 to 2.80).	Potentially severe DDI prevalence: 9427/58 800=16%	Only the interactions identified as severe were considered in these analyses.
20.	Guthrie *et al*, 2015[39]	Scotland, UK	Cross-sectional	311 881 residents aged ≥20 years from the community-dispensed prescribing data (general practice). Living in own home: 308 660.	Prescribed drugs	Potentially serious DDI. Patient characteristics associated with the presence of potentially serious DDI. DDI screening tool: analysis of community-dispensed prescribing data using British National Formulary 2010.	Prescribing error: DDI prevalence: 40 689 adults (13%) had potentially serious DDI in 2010 (for both residents living in own home and care home). Number of patient with potentially serous DDI for residence living in their own home in 2010=13 615.	DDI prevalence: 13 615/308 660=4.4%	Resident living in both care home or own home. Risk factors for own home and care home.
21.	Maio *et al*, 2006[40]	Emilia-Romagna, Italy	Cohort retrospective	849 425 elderly outpatients aged ≥65 years from the Emilia-Romagna outpatient prescription claims database	Prescribed drugs	PIM using the 2002 Beers criteria and factors associated with PIM. Prescription review.	Prescribing error: PIM prevalence: A total of 152 641 (18%) elderly had one or more occurrences of PIM prescribing. Risk factors: 1. Older age (≥85 years) (OR 1.18, 95% CI 1.16 to 1.2, p<0.05). 2. ≥10 drugs prescribed (OR 7.33, 95% CI 7.15 to 7.51, p<0.05). 3. ≥4 chronic conditions (OR 1.76, 95% CI 1.72 to 1.81, p<0.05).	PIM prevalence: 152 641/849 425=18%	

Continued

Table 1 Continued

Key characteristics of included studies

	Author, year	Country/city	Study design/type	Population of interest	Exposure of interest	Outcome of interest	Main finding	Conclusion, n/N (%)	Additional notes
22.	de Oliveira Martins *et al*, 2006[41]	Lisbon, Portugal	Cross-sectional	213 elderly aged ≥65 years from 12 community pharmacies	Prescription and home medications	IDU by 1997 Beers and 2003 Beers explicit criteria. Using survey.	Prescribing error: PIM prevalence: Using the 1997 Beers explicit criteria, 75 occurrences of inappropriate medicines were detected in 59 patients (27.7%). Using the 2003 Beers explicit criteria inappropriate medication was detected in 82 patients (38.5%). Risk factors: The occurrence of inappropriate medicines was significantly associated with the consumption of a high number of drugs.	IDU prevalence: 59/213=27.7% using 1997 Beers IDU prevalence: 82/213=38.5% using 2003 Beers	
23.	Pugh *et al*, 2006[42]	Austin, Texas, USA	Cross-sectional, retrospective	1 096 361 outpatient elderly aged ≥65 years using national data from the Veterans Health Administration	Prescribed drug only	Potentially IP included in the 2006 HEDIS criteria and to determine if patient risk factors are similar to those found using Beers criteria. Using database.	Prescribing error: IP prevalence: Overall, 19.6% of older veterans were exposed to HEDIS 2006 drugs. Risk factors: 1. Patients receiving ≥10 medications were at greatest risk of exposure in men (OR 8.2, 95% CI 8 to 8.4) and women (OR 9.6, 95% CI 8.2 to 11.2). 2. Patients with more outpatient clinic visits (≥10) were at greater risk regardless of gender (OR 1.4, 95% CI 1.3 to 1.6). 3. Diagnosis with other mental illness (eg, depression, anxiety) alone or in combination with serious mental illness was associated with higher risk of potentially IP for women (OR 1.3, 95% CI 1.1 to 1.5).	Potentially IP prevalence: 214 887/1 096 361=19.6%	
24.	Saab *et al*, 2006[43]	Lebanon	Descriptive	277 elderly aged ≥65 years from 10 community pharmacies	Prescription and/or OTC medications	IDU (Beers criteria, missing doses, inappropriate frequency of administration, poor memory, drug–disease interaction, DDI, inappropriate dose, duplicated therapy, discontinuation of therapy, adverse effect and inappropriate indication). Factors that predict potentially inappropriate drug intake. Review patient profile using community pharmacy data and inperson interviews.	Prescribing error: PIM prevalence: The prevalence of elderly outpatient with at least one inappropriate medication: 165/277 (59.6%) (include five patients with ADR). Inappropriate medication use was most frequently identified in terms of Beers criteria (22.4%), missing doses (16.8%) and incorrect frequency of administration (13%). Drug–disease interaction in 28 patients (10.1%), DDI 14 (5.1%), duplicate therapy 12 (4.3%). Risk factors: Female sex (65.7% vs 53.3% for male, p=0.03). There were also significant associations between the likelihood of use of an inappropriate drug and (1) increased number of medical illnesses (p<0.00002); (2) consumption of an OTC drug and/or prescription drug (p=0.048 and p=0.0035, respectively); and (3) consumption of both OTC and prescription drugs (p<0.0002).	IDU prevalence: 62/277=22.4% using Beers criteria	Just extracted the IDU by Beers criteria because the IDU includes 5 cases of ADR and some patients had more than one IDU. Risk factors for all types of IDU.
25.	Zuckerman *et al*, 2006[44]	USA	Cohort retrospective	487 383 community-dweller elderly aged ≥65 years. Data from MarketScan Medicare Supplemental and Coordination of Benefits database.	Prescribed drug	Inappropriate medication use using Beers criteria	Prescribing error: PIM prevalence: 204 083 elderly used inappropriate medication. Use of inappropriate drugs was associated with a 31% increase in risk of nursing home admission, compared with no use of inappropriate drugs (adjusted relative risk 1.31, 99% CI 1.26 to 1.36).	Inappropriate medication use prevalence: 204 083/487 383=41.9%	
26.	Bregnhøj *et al*, 2007[45]	Copenhagen, Denmark	Cross-sectional	212 elderly aged ≥65 years with polypharmacy (≥5 drugs) patients from primary care	Subsidised and non-subsidised medications prescribed	IP measured by the MAI: 10 criteria are indication, effectiveness, dosage, directions practicality, directions correctness, DDI, drug–disease interaction, duplication, duration and expense). Patients exposed to polypharmacy were identified via the database recording the drug subsidy system of Danish pharmacies and questionnaire.	Prescribing error: IP prevalence: The majority of the patients, namely 94.3%, had one or more inappropriate ratings among their medications.	IP prevalence: 200/212=94.3%	
27.	Johnell and Fastbom, 2008[46]	Sweden	Cross-sectional	731 105 people aged ≥75 years from the Swedish Prescribed Drug Register (secondary data analysis)	Prescribed drug only and multidose drug dispensing	Whether the use of multidose drug dispensing is associated with potential IDU (ie, anticholinergic drugs, long-acting benzodiazepines, concurrent use of ≥3 psychotropic drugs and combinations of drugs that may lead to potentially serious DDIs). Information from the Swedish Prescribed Drug Register.	Prescribing error: PIM prevalence: Prevalence of potential IDU in multidose dispensing users: 40.3% (women: 41%, men: 38.5%). Prevalence of potential IDU in prescription users: 13.6% (women: 15%, men: 11.5%). The multidose users had higher prevalence of all indicators of potential inappropriate drug than prescription users. 1. The younger elderly (aged 75–79 years) who used multidose drug dispensing had the highest frequency of all indicators of potential IDU. 2. Most indicators of IDU were more common in women than men. 3. Multidose drug dispensing among those aged 75–79 years old was even more strongly associated with any IDU, anticholinergic drugs, three or more psychotropic drugs in both men and women, and long-acting benzodiazepines among men.	PIM prevalence: Multidose dispensing users: 292 737/731 105=40% Prescription users: 99 430.3/731 105=13.6%	Multidose drug dispensing means that patients get their drugs machine-dispensed into one unit for each dose occasion and packed in disposable bags.

Continued

Table 1 Continued

Key characteristics of included studies

	Author, year	Country/city	Study design/type	Population of interest	Exposure of interest	Outcome of interest	Main finding	Conclusion, n/N (%)	Additional notes
28.	Berdot *et al*, 2009[47]	Dijon, Bordeaux, Montpellier, France	Cohort prospective	6343 community-dwelling elderly aged ≥65 years	Prescribed drug	PIM using 1997 and 2003 Beers criteria, Fick and Laroche. Face-to-face interview using standardised questionnaire.	Prescribing error: PIM prevalence: One-third (31.6%) of the study participants reported using at least one inappropriate medication at study entry.	PIM prevalence: 2004/6343=31.6%, p<0.001	
29.	Haider *et al*, 2009[48]	Sweden	Cross-sectional, register-based study	626 258 older people aged 75–89 years from the Swedish Prescribed Drug Register (secondary data analysis)	Prescribed drug only	If low education associated with potential IDU (ie, anticholinergic drugs, long-acting benzodiazepines, concurrent use of ≥3 psychotropic drugs and clinically relevant potential DDI). Information from the Swedish Prescribed Drug Register.	Prescribing error: PIM prevalence: The proportion of participants reporting use of at least one potential IDU was 34.6%. Risk factors: Subjects with low education had a higher probability of potential IDU (OR 1.09, 95% CI 1.07 to 1.17). Older age, being a woman and higher CCI were associated with the highest frequencies of potential IDU.	IDU prevalence: 216 685/626 258=34.6%	
30.	Lai *et al*, 2009[49]	Taiwan	Descriptive	2 133 864 patients aged ≥65 years between 2001 and 2004 from ambulatory care National Health Insurance claim database	Prescribed drug	PIM prescribing using updated 2003 Beers criteria and the characteristics of and risk factors for such prescribing	Prescribing error: PIM prevalence: A mean of 63.8% of the older population received a PIM at least once a year in 2001–2004. Details: 2001: 1 974 869 patients of whom 1 297 425 had inappropriate prescription (65.7). 2002: 2 026 737 patients of whom 1 312 147 had inappropriate prescription (64.7). 2003: 2 077 677 patients of whom 1 295 227 had inappropriate prescription (62.3). 2004: 2 133 864 patients of whom 1 333 792 had IP (62.5). Risk factors: The only patient characteristic associated with an increased likelihood of the prescribing of PIM was female sex (male sex: OR 0.982 (95% CI 0.980 to 0.983)) (p<0.001) and when ≥4 drugs were prescribed (p<0.001). The following are physician characteristics associated with a greater likelihood of the prescribing of PIM: 1. Male sex (OR 1.206, 95% CI 1.202 to 1.210, p<0.001). 2. Older age (43–50 years: OR 1.021, 95% CI 1.018 to 1.025, p<0.001; ≥51 years: OR 1.238, 95% CI 1.235 to 1.242, p<0.001). 3. Family medicine/general practice (OR 1.267, 95% CI 1.265 to 1.269, p<0.001).	PIM prevalence: 2001: 65.7% 2002: 64.7% 2003: 62.3% 2004: 1 333 792/2 133 864=62.5%	
31.	Ryan *et al*, 2009[50]	Ireland	Cohort prospective	500 patients aged ≥65 years from primary care	Prescribed drug	IP using 2003 Beers criteria and IPET. Screening patients' medical records (electronic and paper).	Prescribing error: PIM prevalence: 65 patients (13%) and 52 patients (10.4%) had at least one medicine prescribed inappropriately using 2003 Beers and IPET criteria, respectively.	IP prevalence: Beers 2003: 65/500=13% IPET: 52/500=10.4%	
32.	Ryan *et al*, 2009[51]	Cork, Southern Ireland	Descriptive case record review	1329 elderly aged ≥65 years from primary care	Prescribed drugs	A—1. PIM using 2003 Beers and STOPP criteria. 2. PPO using START criteria. B—Relationship between age and number of prescription drugs and IP. Case record through paper and electronic record review.	Prescribing error: PIM prevalence: IP rate identified by Beers criteria in 18.3% (243) of patients. IP rate identified by STOPP was 21.4% (284). PPO was identified in 22.7% (302) of patients using the START tool. Risk factors: A significant correlation was found between the occurrence of PIM and the following: 1. The number of medicines prescribed when calculated using Beers criteria (r_s=0.270, p<0.01) and STOPP (r_s=0.356, p<0.01) using Spearman's ρ correlation test. 2. Age using Beers criteria (r_s=0.068, p<0.01) and STOPP (r_s=0.071, p<0.01). 3. Increasing CCI score identified by STOPP (r_s=0.210, p<0.01).	PIM prevalence: Beers: 243/1329=18.3% STOPP: 284/1329=21.4% PPO prevalence: START: 302/1329=22.7%	Spearman's ρ correlation test
33.	Akazawa *et al*, 2010[52]	Tokyo, Japan	Cohort retrospective	6628 elderly patients aged ≥65 years from health insurance claim data (secondary data analysis)	Prescribed drugs	PIM using modified Beers criteria in Japan. Drug utilisation review using medical and pharmacy claim from database of Japan Medical Data Center.	Prescribing error: PIM prevalence: 43.6% (2889/6628) were prescribed at least one PIM. Risk factors: Factors positively associated with PIM prescriptions at a significance level of 5% included the following: hospital admission (OR=3.35, 95% CI 2.43 to 4.62); polypharmacy (OR=5.69, 95% CI 5 to 6.48); prescriptions from a hospital (OR=1.19), general medicine practitioner (OR=1.46) or psychiatrist/neurologist (OR=2.33); and comorbid conditions including peptic ulcer disease without bleeding (OR=4.18, 95% CI 3.52 to 4.97), depression (OR=3.69), cardiac arrhythmias (OR=1.93), other neurological disorders (Parkinson's disease, multiple sclerosis and epilepsy; OR=1.88) and congestive heart failure (OR=1.46). PIM users had significantly higher hospitalisation risk (1.68-fold), more outpatient visit days (1.18-fold) and higher medical costs (33% increase) than did non-users.	PIM prevalence: 2889/6628=43.6%	*Consequence

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Table 1 Continued

Key characteristics of included studies

	Author, year	Country/city	Study design/type	Population of interest	Exposure of interest	Outcome of interest	Main finding	Conclusion, n/N (%)	Additional notes
34.	Zaveri *et al*, 2010[55]	Ahmedabad city, India	Descriptive prospective	407 geriatric patients aged ≥65 years from medicine outpatient department	Prescribed drug	PIM using 2003 Beers criteria. Using prospective proforma data collection.	Prescribing error: PIM prevalence: Out of 407 patients, 96 patients (23.6%) received at least one drug that was potentially inappropriate. Risk factors: There was highly significant association between the number of drugs prescribed and frequency of use of PIMs (p<0.0002).	PIM prevalence: 96/407=23.6%	
35.	Barnett *et al*, 2011[54]	Tayside, Scotland, UK	Cohort	65 742 elderly aged 66–99 years living in home	Prescribed drug	PIM using 2003 Beers criteria and the association between exposure to PIM and mortality. Using dispensing and prescribing database and medical record.	Prescribing error: PIM prevalence: PIM found in 20 304 (30.9%) patients living at home. Risk factors: After adjustment for age, sex and polypharmacy, 1. Patient at increased risk of receiving at least one PIM if they were younger, female and had higher polypharmacy. 2. Receiving at least one PIM was not associated with increased risk of mortality (adjusted OR 0.98, 95% CI 0.92 to 1.05).	PIM prevalence: 20 304/65 742=30.9%	Risk factors for both care home and home
36.	Chang *et al*, 2011[56]	Taipei, Taiwan	Cohort	193 outpatient elderly patients aged ≥65 years with polypharmacy (≥8 chronic medications) from Medication Safety Review Clinic in Taiwanese Elders (MSRC-Taiwan) study	Prescribed drugs and dietary supplement excluding herbals	PIM using six different criteria and drug-related problem: the 2003 version of the Beers criteria (from the USA), the Rancourt (from Canada), the Laroche (from France), STOPP (from Ireland), the Winit-Watjana (from Thailand) and the NORGEP criteria (from Norway). Analyse baseline data from the MSRC-Taiwan study. Secondary data analysis.	Prescribing error: PIM prevalence: The proportion of patients who had at least one PIM varied from 24% (the NORGEP criteria) to 73% (the Winit-Watjana criteria). Approximately 31% (the STOPP criteria) to 42% (the NORGEP criteria) of PIMs identified were considered as drug-related problems by the medication review team experts. Risk factors: In the bivariate analysis, the common characteristics associated with having at least one PIM in all criteria were a high number of chronic conditions and a high number of chronic medications.	PIM prevalence: 24%–73%	
37.	Leikola *et al*, 2011[56]	Finland	Cross-sectional	841 509 non-institutionalised elderly patients aged ≥65 years from Finland's Social Insurance Institution prescription register of all reimbursed drugs for outpatients	Prescribed and OTC medications that are reimbursed	PIM using 2003 Beers criteria	Prescribing error: PIM prevalence: 14.7% (n=123 545) had received PIMs according to the Beers 2003 criteria.	PIM prevalence: 123 545/841 509=14.7%	
38.	Lin *et al*, 2011[57]	Taiwan	Cross-sectional, retrospective analysis	327 elderly patients aged ≥65 years from outpatient clinic of a community health centre	Prescribed drugs	PIM using 2003 Beers criteria and risk factors of PIM use. Using data review.	Prescribing error: PIM prevalence: The prevalence of patients having at least one PIM was 27.5% (90/327). Risk factors: Independent risk factors for PIMs are older age (OR=1.05, 95% CI 1.00 to 1.09, p=0.046), higher number of prescribed medications (OR=1.06, 95% CI 1.39 to 1.98, p<0.001) and diagnosis of acute diseases (OR=8.98, 95% CI 4.71 to 17.1, p<0.001).	PIM prevalence: 90/327=27.5%	
39.	Woelfel *et al*, 2011[70]	California, USA	Cross-sectional	295 elderly aged ≥65 years from ambulatory population of Medicare beneficiaries	Prescribed drug	PIM using 2003 Beers criteria. Using medication review	Prescribing error: PIM prevalence: 54 (18.3% beneficiaries were taking at least one PIM. Risk factors: The number of medications was significantly greater in the PIM than the non-PIM group (p<0.001).	PIM prevalence: 54/295=18.3%	
40.	Zhang *et al*, 2011[58]	USA	Cohort retrospective	3570 elderly community-based respondents aged ≥65 from 2007 MEPS, a nationally representative survey of the US community-dwelling population	Prescribed drug	PIM using Zhan criteria and risk factors for PIM use. Information from MEPS database.	Prescribing error: PIM prevalence: PIM prevalence in 2007: 13.84% (CI 12.52 to 15.17). PIM prevalence in 1996: 21.3% (CI 19.5 to 23.1). Risk factors: Older women, people taking ≥25 prescriptions, people with middle family income, people living in the South census region, and people who said they were in fair or poor health were more likely to have received an inappropriate medication during the year.	PIM prevalence: 13.84%–21.3%	
41.	Haasum *et al*, 2012[59]	Sweden	Cross-sectional, retrospective	1 260 843 home-dwelling elderly aged ≥65 years from the Swedish Prescribed Drug Register	Prescribed drug only	Potentially IDU (use of anticholinergic drugs, long-acting benzodiazepines, concurrent use of ≥3 psychotropics and potentially serious DDIs). Information from the Swedish Prescribed Drug Register.	Prescribing error: PIM prevalence: 11.6% of the home-dwelling elderly were exposed to potentially IDU.	Potentially IDU prevalence: 145 749/1 260 843=11.6%	Information on both institutionalised and home-dwelling. Extracted home-dwelling information only.
42.	Candela Marroquí *et al*, 2012[19]	Cáceres, Spain	Descriptive	471 patients aged ≥65 years from health centres	Consumed medications	Potentially IP using STOPP/START criteria. Using patient interview and medical chart review.	Prescribing error: PIM prevalence: 249 patients (52.8%, 95% CI 48.3 to 57.3) had potentially IP according to STOPP/START criteria. STOPP: 162 patients (34.3%, 95% CI 30.2% to 38.8%). START: 114 patients (24.2%, 95% CI 20.5% to 28.2%).	Potentially IP prevalence: 249/471=52.8% (95% CI 48.3 to 57.3)	

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Table 1 Continued

Key characteristics of included studies

	Author, year	Country/city	Study design/type	Population of interest	Exposure of interest	Outcome of interest	Main finding	Conclusion, n/N (%)	Additional notes
43.	Nyborg *et al*, 2012[60]	Norway	Cross-sectional, retrospective	445 900 home-dwelling elderly aged ≥70 years from the Norwegian Prescription Database	Prescribed drug	Prevalence of and predictors for PIM use by the NORGEP criteria. Survey undertaken based on data from the Norwegian Prescription Database.	Prescribing error: PIM prevalence: 34.8% of the study population was exposed to at least one PIM. Risk factors: The odds of receiving potentially harmful prescriptions increased with the number of doctors involved in prescribing (OR 3.52, 99% CI 3.44 to 3.60 for those with ≥5 compared with those with 1 or two prescribers). Women were at higher risk for PIMs (OR 1.6, 99% CI 1.58 to 1.64).	PIM prevalence: 155 341/445900= 34.8% (99% CI 34.7 to 35)	
44.	Yasein *et al*, 2012[61]	Jordan	Cross-sectional	400 elderly aged ≥65 years from family practice clinic	Prescribed drug	Polypharmacy (≥5 drugs) and IP using 2003 Beers criteria. Using patient file and patient interview.	Prescribing error: PIM prevalence: Inappropriate medications as determined by Beers criteria independent of diagnosis accounted for 118 (29.5%) patients.	IP prevalence: 118/400=29.5%	
45.	Blozik *et al*, 2013[62]	Helsana, Switzerland	Cohort	2008: 1 059 495 2009: 1 047 939 2010: 929 791 Community-dwelling adults aged >18 years from claim data of Helsana	Prescribed drug submitted for reimbursement	Prevalence of polypharmacy and PIM using 2003 Beers criteria or the PRISCUS list. Using analysis of data based on claim data from Switzerland health insurance.	Prescribing error: PIM prevalence: According to 2003 Beers criteria, 10.3% of the community-dwelling population aged >65 years received at least one medication which is PIM, and according to the PRISCUS list 1, 16.0% of persons had a PIM. When using both Beers and PRISCUS criteria, 21.1% of the population received at least one PIM. Of those persons older than 65 years asking for reimbursement of medications, 12.9% received at least one PIM according to 2003 Beers, 20.2% according to PRISCUS and 26.6% of either definition. Risk factors: Women were more likely to receive a PIM: 25.5% of women as compared with 15.4% of men when both Beers and PRISCUS definitions were used.	PIM prevalence: 21.1%	There are huge discrepancies in estimating the prevalence of PIM depending on the definition used.
46.	Cahir *et al*, 2013[63]	Ireland	Cohort retrospective	931 community-dwelling elderly aged ≥70 years from 15 general practices	Prescribed drug and OTC	The association between potentially IP using STOPP and health-related outcomes (ADEs, HRQOL, and hospital accident and ED). Using patient self-report and medical record.	Prescribing error: PIM prevalence: Prevalence of potentially IP was 40.5% (n=377). ADE prevalence: In total, 674 of 859 participants (78%) were classified as having at least one ADE during the study period. Risk factors: Patients with ≥2 potentially IP indicators were: 1. Twice as likely to have an ADE (adjusted OR 2.21, 95% CI 1.02 to 4.83, p<0.05). 2. Significantly lower mean HRQOL utility (adjusted coefficient −0.09, SE 0.02, p<0.001). 3. A twofold increased risk in the expected rate of ED visits (adjusted incidence rate ratio 1.85, 95% CI 1.32 to 2.58, p<0.001).	Potentially IP prevalence: 377/931=40.5% ADE prevalence: 674/859=78%	*Consequence. Type of ADE was not mentioned.
47.	Weng *et al*, 2013[64]	Taiwan	Cross-sectional, retrospective	780 older patients aged ≥65 years from the outpatient geriatric clinic	Long-term prescribed drugs (≥28 days) for chronic diseases, not OTC	Impact of number of drugs prescribed on the risk of PIM using STOPP criteria. Patient medical chart review.	Prescribing error: PIM prevalence: 302 patients (39%) had at least one PIM. Risk factors: Multivariate analysis revealed that PIM risk was associated with the number of medications prescribed (p<0.001) and the presence of cardiovascular (p<0.001) or gastrointestinal disease (p=0.003). Patients prescribed ≥5 drugs (adjusted OR=5.4) had significantly higher PIM risk than those prescribed ≤2 drugs.	PIM prevalence: 302/780=39%	
48.	Zimmermann *et al*, 2013[19]	German	Cohort longitudinal analysis	Follow-up 3: n=1942 Baseline: n=3214 1855 elderly aged ≥75 years from primary care. Data from the prospective, multicentre, observational study 'German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe)'.	Prescribed drug	PIM using Beers, PRISCUS list. By checking medications during visits to patients' homes.	Prescribing error: PIM prevalence: At baseline, PIM prevalence is 29% (848) (according to the PRISCUS list, which decreased to 25.0% (464) 4.5 years later (χ^2: 7.87, p=0.004). The Beers list yielded a prevalence of 21% (620) at baseline, decreasing after 4.5 years to 17.1% (317) (χ^2: 10.77, p=0.000). Risk factors: By PRISCUS list: The risk for PIM increase with: 1. Increasing age of the patients (OR: 1.06, CI 1.00 to 1.13, p=0.037). 2. The presence of depression (OR: 2.42, CI 1.65 to 3.57, p=0.000). 3. Increasing number of prescription drugs (OR: 1.99, CI 1.80 to 2.18, p=0.000). By contrast, the risk of taking PIM decrease by using PRISCUS list with the number of present illness (OR: 0.88, CI 0.80 to 0.97, p=0.012). As the growing number of ingested prescription drugs increased the risk for the ingestion of PIM from the Beers list (OR: 1.66, CI 1.50 to 1.84; p=0.000).	Prescribing error: PIM prevalence: 17%–29%	

Continued

Table 1 Continued

Key characteristics of included studies

	Author, year	Country/city	Study design/type	Population of interest	Exposure of interest	Outcome of interest	Main finding	Conclusion, n/N (%)	Additional notes
49.	Baldoni *et al*, 2014[59]	Ribeirao Preto, Brazil	Cross-sectional	1000 elderly aged ≥60 years from outpatient pharmacy	Prescribed drug, self-medication (309 users) and OTC (802 users)	Prevalence and factors associated with PIM using 2003 and 2012 Beers criteria. Using structured interview questionnaire.	Prescribing error: PIM prevalence: According to Beers criteria 2003, 480 (48.0%) participants used at least one PIM, the mean being 1.38 (SD=0.65) PIMs/person, ranging from 1 to 5. According to Beers criteria 2012, 592 (59.2%) participants used at least one PIM, the mean being 1.56 (SD=0.81) PIMs/person, ranging from 1 to 6. ADE: During the interview 45.5% of participants reported complaints related to ADEs; 94.5% of these were caused by prescribed medication. Risk factors: Factors that are associated with PIMs use were female gender, self-medication, use of OTC medications, complaints related to ADEs, psychotropic medication and more than five medications. *Ten medications with the highest prevalence of self-reported ADEs complaints are clonidine, amitriptyline, metformin, fluoxetine, dexchlorpheniramine, diclofenac, captopril, acetylsalicylic acid, simvastatin and hydrochlorothiazide. Among them, five were considered PIMs according to Beers criteria, of which clonidine, amitriptyline and dexchlorpheniramine are listed in both criteria, while fluoxetine is listed only in Beers criteria 2003 and diclofenac is listed only in Beers criteria 2012.	PIM prevalence by Beers criteria 2003: 480/1000=48.0% PIM prevalence by Beers criteria 2012: 592/1000=59.2%	*Error-related adverse event
50.	Castillo-Páramo *et al*, 2014[65]	Spain	Cross-sectional	272 electronic records of elderly aged ≥65 years from primary healthcare	Prescribed drugs	PIM using STOPP/START criteria and version adapted to Spanish primary healthcare and factors may modulate PIM onset. Using electronic health record and paper clinical record.	Prescribing error: PIM prevalence: The prevalence of PIM (misprescribing and overprescribing) using the STOPP original criteria was 37.5% (95% CI 31.7 to 43.2), and 50.7% (95% CI 44.7 to 56.6) using the STOPP Spanish AP2012 version. The prevalence of underprescribing was 45.9% (95% CI 40.0 to 51.8) with the START original criteria, and 43.0% (95% CI 37.1 to 48.9) with the START AP2012 version. Risk factors: A significant correlation was found between the number of STOPP PIM and age or number of prescriptions, and between the number of START PIM with age, CCI and number of prescriptions.	PIM prevalence: 102/272 (STOPP)=37.5% (95% CI 31.7 to 43.2), 138/272 (STOPP AP2012)=50.7% (95% CI 44.7 to 56.6), 125/272 (START)=45.9%, 117/272 (START AP2012)=43%	
51.	Vezmar Kovačević *et al*, 2014[66]	Serbia Belgrade	Cross-sectional, prospective	509 elderly aged ≥65 years from five community pharmacies	Prescribed drug	PIM and PPO using STOPP/START criteria. Using patient interview and medical, biomedical record.	Prescribing error: PIM prevalence: There were 164 PIMs identified in 139 patients (27.3%) by STOPP and 439 PPOs identified in 257 patients (50.5%) by START. Risk factors: Patients with more than four prescriptions had a higher risk for PIM (OR 2.85, 95% CI 1.97 to 4.14, p<0.001) and ≥9 medications (OR 7.43, 95% CI 3.20 to 17.23, p<0.001). Patients older than 74 years were more likely to have a PPO (75–84 years: OR 1.47, 95% CI 1.01 to 2.13, p=0.041; and ≥85 years: OR 1.79, 95% CI 1.19 to 2.83, p=0.009).	PIM prevalence: 139/509=27.3% PPO prevalence: 257/509=50.5%	
52.	Amos *et al*, 2015[67]	Emilia-Romagna, Italy	Cohort retrospective	865354 elderly aged ≥65 years community-dwelling from administrative care data	Prescribed drug only	PIM using updated Maio criteria and patient characteristics related to IP. Using regional Emilia-Romagna administrative healthcare database.	Prescribing error: PIM prevalence: A total of 240 310 (28%) older adults were exposed to at least one PIM. Risk factors: The oldest group (≥85) followed by patients aged 75–84 had 53% and 25% greater odds of receiving PIM than patients 65–75 years old, respectively (OR=1.53, 95% CI 1.50 to 1.55; OR=1.25, 95% CI 1.23 to 1.26, respectively). These odds of exposure to any PIM were slightly lower among men than women (OR=0.98, 95% CI 0.97 to 1.00). An increase in the number of medications prescribed to the patient corresponded with higher odds of PIM exposure. Older GPs (≥56), male GPs and solo practice GPs were more likely to prescribe PIMs to their older patients.	PIM prevalence: 240 310/865 354=28%	
53.	Hedna *et al*, 2015[68]	Sweden	Cohort retrospective	542 elderly aged ≥65 years from the Swedish Total Population Register (primary care)	Prescribed drug	Prevalence of potentially IPs using STOPP criteria and to investigate the association between potentially IPs and occurrence of ADRs. Using the Swedish Prescribed Drug Register, medical records and health administrative data.	Prescribing error: PIM prevalence: 226 patients using primary healthcare had potentially IP. Risk factors: Persons prescribed potentially IP had more than twofold increased odds to experience ADRs (OR 2.47, 95% CI (1.65 to 3.69), p<0.001), compared with that in persons without potentially IP.	Potentially IP prevalence: 226/542=42%	*Error-related adverse event. The association between PIPs and occurrence of ADRs was for primary care, outpatient or inpatient and hospitalised patients.

Continued

Table 1 Continued

Key characteristics of included studies

	Author, year	Country/city	Study design/type	Population of interest	Exposure of interest	Outcome of interest	Main finding	Conclusion, n/N (%)	Additional notes
54.	Moriarty *et al*, 2015[69]	Ireland	Cohort prospective	2051 elderly aged ≥65 years from The Irish Longitudinal Study on ageing. Community-dwelling elderly.	Prescribed drug only	PIM and PPO using STOPP, Beers criteria, ACOVE indicators and START. Using face-to-face interview, then follow-up after 1 and 2 years.	Prescribing error: PIM prevalence Baseline N (%) (95% CI) / Follow-up N (%) (95% CI) Any PIM using STOPP, Beers, ACOVE: 1259 (61.4%) (CI 59.3 to 63.5) / 1330 (64.8%) (CI 62.8 to 66.9) Any PPO using START, ACOVE: 1094 (53.3%) (CI 51.2 to 55.5) / 1161 (56.6%) (CI 54.5 to 58.8) Both PIM and PPO: 753 (36.7%) / 843 (41.1%) Risk factors: Female sex, age and higher number of medicines were significantly associated with change in PIM prevalence. Age and higher numbers of medicines and chronic conditions were found to be significantly associated with change in PPO prevalence.	PIM: 36.7%–64.8%	
55.	Ramia and Zeenny, 2014[71]	Lebanon	Cross-sectional	284 outpatients aged ≥18 years visiting community pharmacy	Patients on ≥1 of the chronic medications mentioned in the study	The completion of therapeutic/safety monitoring tests. Patients were subjected to a questionnaire assessing the appropriateness of their laboratory-test monitoring.	Monitoring error: 1. 185 of the patients (65%) were found to complete some, but not all, of the recommended therapeutic/safety monitoring tests. 2. 76 of the patients (27%) completed all recommended therapeutic/safety monitoring. 3. 23 of the patients (8%) did not complete any of the recommended monitoring tests.	Incomplete therapeutic/safety laboratory-test monitoring prevalence: 208/284=73%	
Other: discrepancies									
56.	Tulner *et al*, 2009[91]	Amsterdam, The Netherlands	Descriptive prospective	120 elderly aged >65 years from Dutch geriatric outpatient	Using more than one prescribed or OTC medications	1. Frequency and relevancy of discrepancies in drug use. 2. Frequency of MDAPEs. 3. Contributing factors such as increasing age, cognitive status and depressive symptoms, the number of medications used, and the number of physicians visited by the patient. By comparing the medication described by the patient and caregivers with the drugs listed by their GP.	Other: discrepancies prevalence: At least one discrepancy (deletion, addition or difference in dosage) between the medication lists from the patient, the GP or the pharmacy was present in 104 patients (86.7%) involving 386 drugs. MDAPES: MDAPES were identified in 29 patients (24.2%). 7 patients had undertreatment due to deletions. 9 patients had ADR due to additions. 13 patient had DDI. Risk factors: Patients with ≥1 discrepancy reported using a higher mean number of drugs (5.9 vs 4.0; p<0.05) and had more prescribing physicians in addition to their GP (1.1 vs 0.43; p<0.05). Both the presence of discrepancies (Pearson's r', 0.293; p=0.05) and MDAPEs (Pearson's r', 0.230; p=0.012) were significantly correlated with the number of medications reported by the patient. *The highest rates of discrepancies were seen for acetaminophen (86.7%), laxatives (82.9%) and formulations for dermatological or ophthalmological diseases (81.3%).	Discrepancies prevalence: 104/120=86.7% *Error-related adverse event: MDAPEs: 29/120=24.2%	*Error-related adverse event

Continued

Table 1 Continued

Key characteristics of included studies

	Author, year	Country/city	Study design/type	Population of interest	Exposure of interest	Outcome of interest	Main finding	Conclusion, n/N (%)	Additional notes
57.	Cornu *et al*, 2012[32]	Brussels, Belgium	Cohort retrospective	189 elderly aged ≥65 years discharged from acute geriatric department of a Belgian university hospital	Prescribed drug	Incidence and type of discrepancies between the discharge letter for the primary care physician and the patient discharge medication and identify possible patient-related determinants for experiencing discrepancies. Discrepancies were categorised as omitted drug, unintended continuation (discontinued home medication documented as home medication), discrepant dose, missing dose, and discrepant brand, omission of a brand name, discrepant frequency, missing frequency or an incorrect pharmaceutical form. By comparing the medications listed in the discharge letter for the primary care physician with those in the patient discharge medication list.	Other: discrepancies prevalence: Almost half of these patients (n=90, 47.6%) (95% CI 40.5 to 54.7) had one or more discrepancies in medication information at discharge. *Two discrepancies (1.2%) were categorised as having the potential to cause severe patient harm. These discrepancies consisted of a wrong dose (doubled the prescribed dose) of digoxin in the patient discharge medication list and the listing of a low-molecular-weight heparin in the patient discharge medication list that was intentionally omitted in the discharge letter because of the development of heparin-induced thrombocytopaenia during hospitalisation. Risk factors: The explorative multivariate model adjusted for age, sex, length of hospital stay and residential situation showed that when the discharge letter contained more than five drugs, the likelihood of experiencing one or more drug discrepancies was 3.22 (95% CI 1.40 to 7.42, p=0.006) times higher than when five or fewer drugs were mentioned. Increasing numbers of drugs in the discharge medication list (OR 1.19, 95% CI 1.07 to 1.32, p=0.001) and discharge letter (OR 1.18, 95% CI 1.07 to 1.32, p=0.001) were associated with a higher risk for discrepancies.	Discrepancies prevalence: 90/189=47.6% (95% CI 40.5 to 54.7)	*Error-related adverse event
Preventable ADEs									
58.	Field *et al*, 2007[77]	USA	Cohort	30000 elderly ≥65 years from ambulatory care	Prescribed drug	ADE resulting from patients error and risk factors. By electronic tracking of administrative data, review of medical records, reports from clinicians, hospital discharge summaries and ED visit.	Preventable ADE: ADE resulting from patients' error prevalence: 113 individuals experienced ADE and potential ADE. Risk factor: In a multivariate analysis, there was a dose-response association between patient errors leading to ADEs and potential ADEs and regularly scheduled medications; compared with zero to two medications, the OR for three to four medications was 2.0 (95% CI 0.9 to 4.2); for five to six medications was 3.1 (95% CI 1.5 to 7.0); and for seven or more medications was 3.3 (95% CI 1.5 to 7.0). The strongest association was with the CCI; compared with a score of 0, the OR for a score of 1–2 was 3.8 (95% CI 2.1 to 7.0); for a score of 3–4 was 8.6 (95% CI 4.3 to 17.0); and for a score of 5 or more was 15.0 (95% CI 6.5 to 34.5).	ADE resulting from patients' error prevalence: 113/3000=0.38%	*ADE resulting from patients' error
59.	Gandhi *et al*, 2010[52]	Boston and Indianapolis, USA	Cross-sectional	68013 outpatients, mean age 48 and 47 years	Prescribed drug	ADE. Using electronic health record screening, chart review and ADE monitor.	Preventable ADE incidence: The overall rate was 138 ADEs/1000 person-years across the two sites. Preventable ADEs rate 15/1000person-years across two sites. *Most common drugs associated with preventable ADE were ACE inhibitors and beta-blockers.	Preventable ADEs rate 15/1000 person-years across two sites	*Preventable ADE
60.	Obreli-Neto *et al*, 2012[26]	Ourinhos microregion, Brazil	Cohort prospective	433 elderly aged ≥60 years from the primary public health system	Prescribed drugs both within and across prescriptions	DDI-related ADR incidence and factors. Using phone or face-to-face structured interview. DDI screening tool: DDI checker programmes (DrugDigest, Drugs, Micromedex and Medscape).	Preventable ADE: DDI-related ADR incidence: occurred in 30 patients (6.9%). Gastrointestinal bleeding occurred in 37% of the DDI-related ADR cases, followed by hyperkalaemia (17%) and myopathy (13%). Seventeen DDI-related ADRs were classified as severity level 2, and hospital admission was necessary in 11 cases. *Warfarin was the most commonly involved drug (37% of cases), followed by acetylsalicylic acid (17%), digoxin (17%) and spironolactone (17%). Risk factors: The multiple logistic regression showed that the following were associated with the occurrence of DDI-related ADRs: 1. Age ≥80 years (OR 4.4, 95% CI 3.0 to 6.1, p<0.01). 2. CCI≥4 (OR 1.3, 95% CI 1.1 to 1.8, p<0.01). 3. Consumption of five or more drugs (OR 2.7, 95% CI 1.9 to 3.1, p<0.01). 4. Use of warfarin (OR 1.7, 95% CI 1.1 to 1.9, p<0.01).	Incidence of DDI-related ADR: 30/433=6.9%	*Error-related adverse event

ACOVE, Assessing Care of Vulnerable Elders; ADE, adverse drug event; ADI, adverse drug interaction; ADR, adverse drug reaction; CCI, Charlson Comorbidity Index; DDI, drug-drug interaction; ED, emergency department; GP, general practitioners; HEDIS, Health Plan Employer Data and Information Set; HRQOL, health-related quality of life; IDU, inappropriate drug use; IP, inappropriate prescribing; IPET, improved prescribing in the elderly tool; MAI, Medication Appropriate Index; MDAPE, medication discrepancy adverse patient event; MEPS, Medical Expenditure Panel Survey; NORGEP, Norwegian General Practice; OTC, over-the-counter; PDDI, potential drug–disease interaction; PIM, potentially inappropriate medicine; PPO, potential prescribing omissions; START, Screening Tool to Alert doctors to Right Treatment; STOPP, Screening Tool of Older Person's Prescriptions.

Table 2A Systematic review quality assessment: Joanna Briggs Institute Critical Appraisal Checklist for descriptive/case series and cross-sectional

		1	2	3	4	5	6	7	8	9	Overall appraised	
1	Ramia and Zeenny, 2014[71] Adult	Y	Y	N	N	NA	NA	Y	Y	Y	High	Patients were subjected to a questionnaire assessing the appropriateness of their laboratory-test monitoring, may cause recall bias.
2	Sorensen *et al*, 2006[76] Adult	Y	Y	N, risk factors related to patient not studied	Y	NA	NA	Y	Y	Y	High	
3	Vuong and Marriott, 2006[25] Adult	U	Y	N	Y	NA	NA	N	Y	Y, percentage was used but statistics was not described in the full text.	High	Unclear sampling strategy.
4	Adams *et al*, 2009[72] Adult	Y	Y	Y (but for all types of adverse event)	N (self-reported adverse events)	NA	NA	N	Y	Y	High	Risk of recall bias and attribution with self-reported adverse events.
5	Gandhi *et al*, 2010[22] Adult	U	Y	N	Y	Y	NA	NA	Y	Y	High	
6	Lu and Roughead, 2011[20] Adult	Y	Y	Y	N (subjective patient-reported medication error)	Y	NA	NA (secondary analysis)	N (telephone survey, self-reported)	Y	High	Risk of recall bias with patient-reported medication error.
7	Sears *et al*, 2012[21] Adult	Y	Y	Y	N (subjective self-reported medication error)	Y	NA	NA (secondary analysis)	N (telephone survey, self-reported)	Y	High	Risk of recall bias with patient self-reported medication error.
8	Koper *et al*, 2013[23] Adult	N (convenience)	Y	N	Y	NA	NA	NA (100% participants)	Y	Y	High	Selection bias.
9	Dallenbach *et al*, 2007[24] Adult-DDI	N (consecutive)	N	N	Y	NA	NA	NA (retrospective)	Y	Y	Moderate	
10	Indermitte *et al*, 2007[34] Adult-DDI	Y (pharmacy choose); N (first 12 customers)	Y	N	Y	NA	NA	Y	Y	Y	High	
11	Mahmood *et al*, 2007[35] Adult-DDI	Y	Y	N	Y	NA	NA	NA (retrospective)	Y	Y	High	Patients may actually be on other drugs so may not catch all the DDI.
12	Guthrie *et al*, 2015[39] Adult-DDI	Y	Y	Y (but for both own home and care home)	Y	Y	NA	NA (secondary analysis)	Y	Y	High	Risk factors for both own home and care home.
13	de Oliveira Martins *et al*, 2006[41] Elderly-PIM	N (first came to pharmacy carrying prescription for two or more drugs)	Y	Y, but not all	Y	Y	NA	N	Y	Y	High	Self-reported data from elderly concerning drug use may lead to information bias.
14	Pugh *et al*, 2006[42] Elderly-PIM	Y	Y	Y	Y	Y	NA	NA (secondary data analysis)	Y	Y	High	May underestimate the exposure because they do not account for OTC.
15	Saab *et al*, 2006[43] Elderly-PIM	Y	Y	Y	Y	NA	NA	Y	Y	Y	High	Self-reported data from elderly concerning drug use may decrease accuracy.

Continued

Table 2A Continued

		1	2	3	4	5	6	7	8	9	Overall appraised	
16	Bregnhøj *et al*, 2007[45] Elderly-PIM	N (each GP was asked to recruit six patients who were randomly selected)	Y	N	Y	NA	NA	Y	Y	Y	High	Selection bias.
17	Johnell and Fastbom, 2008[46] Elderly-PIM	Y	Y	Y	Y	Y	NA	Y	Y	Y	High	Did not look for comorbidity as a risk factor because data were from Swedish Prescribing Drug Register.
18	Haider *et al*, 2009[48] Elderly-PIM	Y	Y	Y	Y	NA	NA	NA	Y	Y	High	
19	Lai *et al*, 2009[49] Elderly-PIM	Y	Y	Y	Y	NA	NA	NA (secondary analysis)	Y	Y	High	Did not address comorbidity as a risk factor.
20	Ryan *et al*, 2009[51] Elderly-PIM	Y	Y	Y	Y	NA	NA	N	Y	Y	High	May underestimate the outcome because they do not account for OTC.
21	Zaveri *et al*, 2010[53] Elderly-PIM	U	Y	Y	Y	NA	NA	N	Y	Y	High	Not enough information in the article.
22	Leikola *et al*, 2011[56] Elderly-PIM	Y	Y	N	Y	NA	NA	NA	Y	Y	High	May underestimate the outcome because database lacks diagnostic patient data, therefore used the Beers 2003 criteria independent of diagnoses and the data provide no information on the use of PIMs that are not reimbursable. Nine PIMs that were not reimbursable in Finland in 2007: triazolam, belladonna alkaloids, diphenhydramine, hydroxyzine, ferrous sulfate, bisacodyl, nitrofurantoin and clonidine.
23	Lin *et al*, 2011[57] Elderly-PIM	U	Y	Y	Y	NA	NA	NA	Y	Y	High	
24	Woelfel *et al*, 2011[70] Elderly-PIM	Y	Y	Y	Y	NA	NA	NA	Y	Y	High	
25	Haasum *et al*, 2012[59] Elderly-PIM	Y	Y	N	Y	Y	NA	NA (secondary data analysis)	Y	Y	High	
26	Nyborg *et al*, 2012[60] Elderly-PIM	Y	Y	Y	Y	Y	NA	NA (secondary data analysis)	Y	Y	High	
27	Yasein *et al*, 2012[61] Elderly-PIM	N	Y	N	Y	Y	NA	N	Y	Y	Moderate	
28	Candela Marroquín *et al*, 2012[19] Elderly-PIM	N (convenience sample)	Y	N	Y	NA	NA	N	Y	Y	Moderate	Sampling strategy. Subjective information on socioeconomic and clinical variables may decrease accuracy.
29	Weng *et al*, 2013[64] Elderly-PIM	Y	Y	Y	Y	Y	NA	N	Y	Y	High	Sampling strategy.
30	Baldoni *et al*, 2014[29] Elderly-PIM	U	Y	Y	Y	Y	NA	Y	Y	Y	High	

Continued

Table 2A Continued

		1	2	3	4	5	6	7	8	9	Overall appraised	
31	Castillo-Páramo *et al*, 2014[65] Elderly-PIM	Y	Y	Y	Y	Y	NA	Y	Y	Y	High	Electronic health record use limitations (incomplete record and quality of data).
32	Vezmar Kovačević *et al*, 2014[66] Elderly-PIM	Y	Y	Y	Y	NA	NA	N	Y	Y	High	
33	Nobili *et al*, 2009[38] Elderly-DDI	Y	Y	Y	Y	NA	NA	NA (administrative database)	Y	Y	High	The use of administrative database limits looking for comorbidity as a confounder.
34	Secoli *et al*, 2010[30] Elderly-DDI	U	Y	Y	Y	NA	NA	NA	Y	Y	High	May underestimate the true DDI prevalence because they do not account for OTC.
35	Obreli Neto *et al*, 2012[27] Elderly-DDI	Y	Y	Y	Y	NA	NA	NA (data from primary healthcare system)	Y	Y	High	May underestimate the DDI prevalence because (1) most instruments available for assessing DDIs consider only pairs of drugs and do not account for interactions involving combinations of three or more drugs so (2) did not account for OTC.
36	Pit *et al*, 2008[74] Elderly	Y	Y	Y	Y	NA	NA	Y	Y	Y	High	
37	Tulner *et al*, 2009[31] Elderly	N (consecutive)	Y	Y	Y	NA	NA	Y	Y	Y	High	Information on medication described by the patient and caregivers may not always be accurate.
38	Obreli Neto *et al*, 2011[26] Elderly-DDI	Y	Y	N	Y	NA	NA	NA	Y	Y	High	
39	Mira *et al*, 2013[73] Elderly	Y	Y	Y	Y	NA	NA	Y	Y	Y	High	Self-reported medication error from elderly concerning drug use may have recall bias.
40	Mand *et al*, 2014[33] Elderly	Y	Y	Y	Y	NA	NA	NA	Y	Y	High	

1 Was study based on a random or pseudo-random sample?
2 Were the criteria for inclusion in the sample clearly defined?
3 Were confounding factors identified and strategies to deal with them stated?
4 Were outcomes assessed using objective criteria?
5 If comparisons are being made, was there sufficient descriptions of the groups?
6 Was follow-up carried out over a sufficient time period?
7 Were the outcomes of people who withdrew described and included in the analysis?
8 Were outcomes measured in a reliable way?
9 Was appropriate statistical analysis used?
DDI, drug-drug interaction; GP, general practitioner; N, no; NA, not applicable; OTC, over-the-counter; PIM, potentially inappropriate medication; U, unclear; Y, yes.

Table 2B Systematic review quality assessment: Critical Appraisal Skills Programme for cohort study

	Study design: cohort															
	Reference	Quality domains														Overall quality
		1	2	3	4	5(a)	5(b)	6(a)	6(b)	7	8	9	10	11	12	
		Are the results of the study valid?								What are the results?			Will the results help locally?			
1	Maio *et al*, 2006[40] PIM	Y	Y	Y	Y	Y, age, gender, geographical location, number of medication, number of chronic condition and income None	N	Y	Y (1 year) retrospective	PIM prevalence: 18%. Older age, polypharmacy and greater number of chronic conditions were significant predictors of PIM use.	P<0.05, 95% CI	Y	Y	Y	–	Moderate
2	Zuckerman *et al*, 2006[44] PIM	Y	Y	Y	Y	Y, but used for irrelevant outcome -	Y	Y	Y (2 years)	Inappropriate medication use prevalence: 41.9%	P=0.01, 99% CI	Y	Cannot tell (generalisability)	Y	Limited information from the database. Confounding factors were for the nursing home admission rather than for PIM.	Moderate
3	Field *et al*, 2007[77] Elderly	Y	Y	Y	Y	Y, age, gender, comorbidity, number of medications None	Y	Y	Y (1 year)	ADE resulting from patients' error prevalence: 0.38%	P<0.05	Y	Y	Y	Possible drug-related incidence for which necessary information was not documented in the medical record was not considered.	High
4	Gagne *et al*, 2008[36] DDI	Y	Y	Y	Y	Y, age, gender, geographical location, comorbidity, number of medication prescribed None	Y	Y	Y (1 year)	DDI: prevalence: 53%	95% CI	Y	Y	Y	Applying the US list of clinically important DDI to Italy may underestimate the prevalence as it captured only 12 out of the 25 DDI original list. Unable to extract risk factors data as it is for all age groups.	High
5	Berdot *et al*, 2009[47] Elderly-PIM	Y	Y	Y	Y	Y, but for irrelevant outcome –	Y	Y	Y (4 years)	PMI prevalence: 31.6%	95% CI, p<0.05	Y	Y	Y	Self-report and data from healthcare insurance plan are not perfect for actual drug consumption. Recall bias. Confounding factors were for the risk of falls rather than for PIM.	High
6	Lapi *et al*, 2009[37] Elderly-PIM	Y	Y	Y	Y	Y, comorbidity, polypharmacy, stroke, heart failure Age, gender	Y	Y	Y (1 year)	1999: IP prevalence: 5.1% Potential DDI prevalence: 30.5% Potential major DDI: 5.6% Polypharmacy was a predictor of PIM use.	P<0.05, 95% CI	Y	N	Y	Self-reported diagnosis and medication use may cause recall bias. Beers list cannot be fully applied to Italy; it most reflects US drug market.	Moderate
7	Ryan *et al*, 2009[50] Elderly-PIM	Y	Y	Y	Y	N –	Cannot tell	Y	Y (6 months)	Medicine prescribed inappropriately. Beers 2003: 13% IPET: 10.4%	Cannot tell	Y	Y	Y	–	Low

Continued

Table 2B Continued

	Study design: cohort														
	Reference	Quality domains													
		1	2	3	4	5(a)	5(b)	6(a)	6(b)	7	8	9	10	11	12	Overall quality
8	Akazawa *et al*, 2010[52] Elderly-PIM	Y	Y	Y	Y	Y, age, gender, polypharmacy (>5 drugs), hospitalisation, comorbidities None	Y	Y	Y (1 year)	Prevalence of PIM: 43.6%. Inpatient service use, polypharmacy and comorbidities were significant predictors of PIM use.	95% CI, p<0.05	Y	Y	Y	Medical information cannot be taken from claim data, unobserved confounder. PIM not associated with age as several other studies.	High
9	Barnett *et al*, 2011[54] Elderly-PIM	Y	Y	Y	Y	Y, age, sex, polypharmacy and place of residence Comorbidity	Y	Y	Y (2 years)	PIM prevalence: 30.9%. Patients at increased risk of receiving at least one PIM if they were younger, female and had higher polypharmacy.	95% CI	Y	Y	Y	Comorbidity not accounted for. Risk factors for both care home and home.	High
10	Chang *et al*, 2011[55] Elderly-PIM	Y	Y	Y	Y	Y, age, sex, education, number of chronic medication, number of chronic conditions and number of ED visits None	Y	Y	Y (12, 24 weeks)	PIM: 24%–73% Number of chronic drugs and number of chronic conditions were a common risk factor in all criteria.	P<0.05	Y	Y	Y	May underestimate the prevalence because several drugs in Taiwan were not available in the sex criteria.	High
11	Zhang *et al*, 2011[58] Elderly-PIM	Y	Y	Y	Y	Y, race, gender, family income, educational level, census region, number of prescription, self-rated health status None	Y	Y	Cannot tell	Prevalence of PIM was from 13.84% (95% CI 12.52 to 15.17) to 21.3% (95% CI 19.5 to 23.1).	95% CI, p<0.05	Y	Y	Y	Recall bias due to self-reported survey. Did not assess DDI and underuse so may underestimate the prevalence.	Moderate
12	Cornu *et al*, 2012[32] Elderly	Y	Y	Y	Y	Y, age, gender, residential situation before admission, residential situation after discharge, number of drugs in the discharge letter or list Comorbidity	Y	Y	Y (from admission to discharge)	Almost half of these patients (47.6% (95% CI 40.5 to 54.7)) had one or more discrepancies in medication information at discharge.	95% CI, p<0.05	Y	Cannot tell	Y	Was done in one centre that may have different procedure of discharge.	Moderate

Continued

Table 2B Continued

	Study design: cohort														
	Reference	Quality domains													Overall quality
		1	2	3	4	5(a)	5(b)	6(a)	6(b)	7	8	9	10	11	12	
13	Mosher *et al*, 2012[75] Elderly	Y	Y	Y	Y	Y, health literacy Age, number of medications, comorbidity	Y	Y	Y (3 and 12 months)	ADEs occurred in 51 patients (16.5%) of the patients within the first 3 months of the study, which increased to 119 patients (38.4%) over the full 12-month follow-up period.	P<0.05	Y	Cannot tell	Y	Results may be biased due to sampling strategy.	Moderate
14	Obreli-Neto *et al*, 2012[28] DDI	Y	Y	Y	Y	Y None	Y	Y	Y (4 months)	Incidence of DDI-related ADR (6.9%)	95% CI, p<0.05	Y	Y	N	Recall bias from weekly meeting with patient. Most instruments available for assessing DDIs consider only pairs of drugs and do not account for interaction involving combinations of three or more drugs so the risk of DDI may be underestimated.	Moderate
15	Blozik *et al*, 2013[62] Adult	Y	Y	Y	Y	Y, gender Age, number of medications, number of disease	Y	Y	Y (3 years)	Prevalence of PIM: 21.1%	95% CI	Y	Y	Y	–	High
16	Cahir *et al*, 2014[63] Elderly-PIM	Y	Y	Y	Y	Y, age, gender, socioeconomic status, private health insurance, comorbidity, number of repeat drug, social support and network, adherence None	Y	Y	Y (6 months) retrospective study	Prevalence of potentially IP was 40.5%.	95% CI	Y	N	Y	Recall bias due to self-reported ADE	Moderate
17	Zimmermann *et al*, 2013[18] Elderly-PIM	Y	Y	Y	Y	Y, gender age, number of medications, number of disease, depression, education None	Y	Y	Y (4.5 years)	At baseline PIM prevalence is 29% (848) according to the PRISCUS list, which decreased to 25.0% (464) 4.5 years later and 21% according to the Beers list decreasing after 4.5 years to 17.1% (317).	95% CI, p<0.05, OR and CI for risk factors	Y	Y	Y	–	High

Continued

Table 2B Continued

	Study design: cohort														
	Reference	Quality domains													
		1	2	3	4	5(a)	5(b)	6(a)	6(b)	7	8	9	10	11	12	Overall quality
18	Amos *et al*, 2015[67] Elderly-PIM	Y	Y	Y	Y	Y, age, gender, geographical location, number of medication Number of chronic conditions	Y	Y	Y (1 year) retrospective study	PIM prevalence 28%, and older age, female, number of medications increase risk of PIM	95% CI, p<0.05	Y	Cannot tell	Y	May underestimate the true PIM prevalence because they do not account for OTC.	Moderate
19	Hedna *et al*, 2015[68] Elderly-PIM	Y	Y	Y	Y	N Age, gender, number of medication, number of chronic condition	Y	Y	Y (3 months) retrospective	Potentially IP prevalence: 42% ADR caused by potentially IP.	95% CI, p<0.05	Y	Cannot tell	Y	Undetected confounders	Moderate
20	Moriarty *et al*, 2015[69] Elderly-PIM	Y	Y	Y	Y	Y, age, gender, number of medication, number of chronic condition, level of education	Y	Y	Y (1 year)	PIM prevalence: 36.7%–64.8%. Female, age and higher number of medicines were associated with change in PIM prevalence. Age and higher numbers of medicines and chronic conditions were found to be associated with change in PPO prevalence.	95% CI	Y	Y	Y	Lack of information on OTC from the pharmacy claim data.	High

1 Did the study address a clearly focused issue?
2 Was the cohort recruited in an acceptable way?
3 Was the exposure accurately measured to minimise bias?
4 Was the outcome accurately measured to minimise bias?
5(a) Have the authors identified all important confounding factors? List the ones you think might be important, that the author missed.
5(b) Have they taken account of the confounding factors in the design and/or analysis?
6(a) Was the follow-up of subjects complete enough?
6(b) Was the follow-up of subjects long enough?
7 What are the results of this study?
8 How precise are the results?
9 Do you believe the results?
10 Can the results be applied to the local population?
11 Do the results of this study fit with other available evidence?
12 What are the implications of this study for practice?
ADE, adverse drug event; ADR, adverse drug reaction; ATC, Anatomical Therapeutic Chemical ; DDI, drug–drug interaction; ED, emergency department; IP, inappropriate prescribing; IPET, improved prescribing in the elderly tool; N, no; OTC, over-the-counter; PIM, potentially inappropriate medication; PPO, potential prescribing omission, U, unclear ;Y, yes.

Person's Prescriptions criteria. Johnell and Fastbom[46] and Haider *et al* mentioned two other specific criteria.[46 48]

B. The prevalence of potential prescribing omission (PPO) was measured in five studies for the elderly age group only (≥65 years), ranging from 23% to 57%.[19 51 65 66 69] PPO was detected by the Screening Tool to Alert doctors to Right Treatment and Assessing Care of Vulnerable Elders.

Dosing errors

Koper *et al*[23] found that overdosing and/or underdosing was found in 44% of patients.[23]

Monitoring errors

Monitoring errors were measured in one study by Ramia and Zeenny,[71] who found that 73% of patients had incomplete therapeutic/safety laboratory-test monitoring tests.[71]

Other errors: discrepancy

One study found that at least one discrepancy between the medication lists from the pharmacy, the GP or the patient was present in 86.7% of patients.[31] In another study, almost half of the patients (47.6%; 95% CI 40.5 to 54.7) had one or more discrepancies in medication information at discharge.[32]

The reported point or period prevalence of medication errors in the community settings, including self-reported medication errors, prescribing errors (indication, drug–disease interaction, DDI, dosing error and inappropriate prescribing), monitoring error and discrepancies, had a very wide range from 2% to 94%. Figure 2 shows the medication errors prevalence estimates stratified according to the settings. The highest prevalence was in primary healthcare or general practice (94%).

RISK FACTORS

Risk factors for medication errors were either related to patients, healthcare professionals and/or medications.

Patient-related risk factors

Patient-related risk factors for the development of medication errors were discussed in 33 studies.[18 20 27 29–33 37 38 40–43 48 49 51–53 55 57 58 60 62 64–67 69 70 73–75]

Seven risk factors related to patients were addressed in the included studies: polypharmacy, increased age, number of diseases or comorbidities, female, low level of education, hospital admission and middle family income (table 3).

Several definitions of polypharmacy existed, ranging from prescription of at least three to six medications concurrently. Twenty-six studies showed a positive association between medication error and polypharmacy,[18 27 29–33 37 38 40–42 49 51–53 55 57 58 64–67 69 70 74] of which 18 mentioned the estimated OR ranging from 1.06 to 11.45.[18 27 29 30 32 33 37 38 40 42 49 52 57 64–67 69]

Older age (≥75 years) was associated with medication errors in 13 studies,[18 27 33 38 40 48 49 51 57 65–67 69] of which 10 mentioned the OR ranging from 1.02 to 4.03.[18 27 33 38 40 49 57 66 67 69]

Healthcare professional-related risk factors

Nine risk factors related to healthcare professionals for the development of medication errors were identified: more than one physician involved in their care, family medicine/GP specialty, age ≥51 years, male GP, frequent changes in prescription, not considering the prescription of other physicians, inconsistency in the information and outpatient clinic visits (see table 4).[27 31 42 49 52 60 67 73 74]

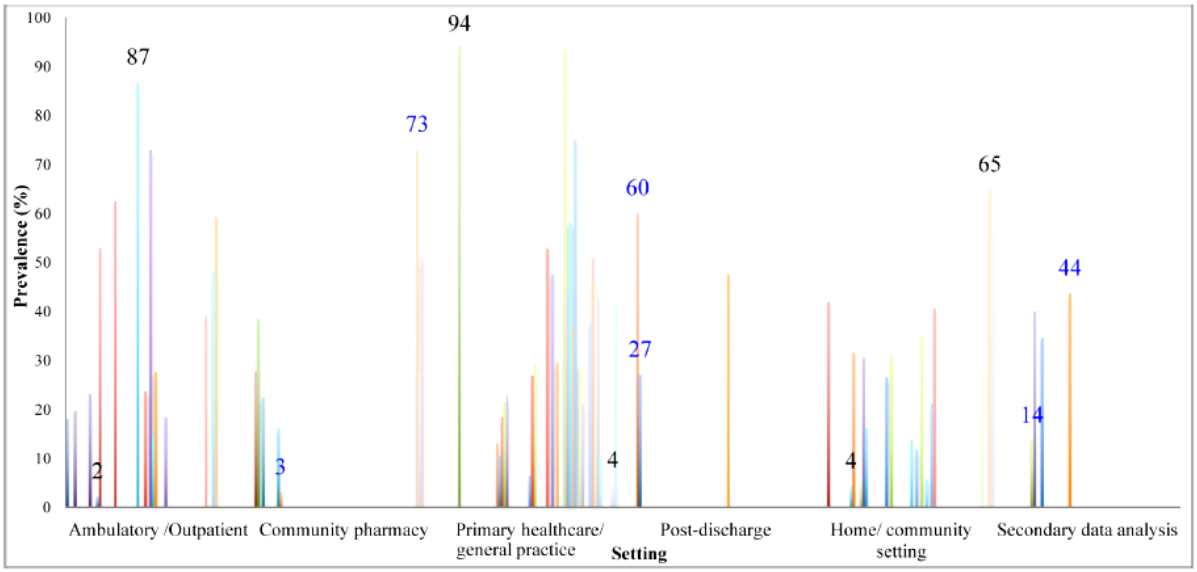

Figure 2 Medication errors prevalence estimates according to settings.

Table 3 Medication errors patient-related risk factors

Risk factor	Studies with positive association (n)	Controlled studies (n)	Controlled for	Specific information	OR or RR (95% or 99% CI) p values
Age ≥75 years	13 (24, 33, 37, 42, 44, 52, 53, 55, 61, 69–71, 73)	10	NA	≥80 years	OR 1.021 (95% CI 1.018 to 1.023) p<0.001[49]
			Adjusted for age, sex, number of regular medicine and diagnosed chronic condition	Older age	OR 1.03 (95% CI 1.02 to 1.04) p<0.05[69]
			NA	Older age	OR 1.05 (95% CI 1 to 1.09) p=0.046[57]
			NA	Older age	OR 1.06 (95% CI 1.0 to 1.13) p=0.037[18]
			NA	≥75 years	OR 1.10 (95% CI 1.05 to 1.15) p<0.001[33]
			NA	≥85 years	OR 1.18 (95% CI 1.16 to 1.20) p<0.05[40]
			Adjusted for sex, age and number of chronic drugs	≥85 years	OR 1.52 (95% CI 1.46 to 1.6)[38]
			NA	≥85 years	OR 1.53 (95% CI 1.5 to 1.55) p<0.01[67]
			NA	≥85 years	OR 1.79 (95% CI 1.19 to 2.83) p=0.009[66]
			Adjusted for sex and age	≥75 years	OR 4.03 (95% CI 3.79 to 4.28) p<0.001[27]
Comorbidity or number of disease or chronic condition drug group (CCDG) score ≥4	10 (24, 26, 33, 44, 47, 56, 59, 73, 77, 78)	3	Adjusted for age, sex, number of regular medicines and diagnosed chronic condition	Higher number of chronic conditions	PPO: OR 1.47 (95% CI 1.39 to 1.56) p<0.05[69]
			NA	CCDG score ≥4	OR 1.76 (95% CI 1.72 to 1.81) p<0.05[40]
			Adjusted for age and sex	Diagnosed disease ≥3	OR 6.43 (95% CI 3.25 to 12.44) p<0.001[27]
CCI	3 (52, 55, 69)	1	NA	CCI <2	RR 2.885 (95% CI 1.972 to 4.22) p=0[65]
Female gender	10 (33, 35, 47, 52, 53, 62, 64, 66, 71, 73)	4	Adjusted for age, sex, number of regular medicines and diagnosed chronic condition		PIM: OR 1.27 (95% CI 1.07 to 1.5) p<0.05[69]
			Adjusted		OR 1.6 (99% CI 1.58 to 1.64)[60]
			Adjusted for age, sex, education level, partnership, per capita income and occupation		Beers 2003: OR 2.5 (95% CI 1.9 to 3.5) Beers 2012: OR 1.8 (95% CI 1.3 to 2.5)[29]
			Adjusted for sex and age		OR 2.49 (95% CI 2.29 to 2.75) p<0.001[27]
Health literacy or low education	2 (52, 79)	1	Adjusted for age, sex, type of residential area and comorbidity		OR 1.09 (95% CI 1.07 to 1.17)[48]
Hospital admission	2 (26, 56)	1	NA		OR 3.35 (95% CI 2.43 to 4.62) p<0.05[52]
Middle family income	1 (62)	NA	NA		

Continued

Table 3 Continued

Risk factor	Studies with positive association (n)	Controlled studies (n)	Controlled for	Specific information	OR or RR (95% or 99% CI) p values
Polypharmacy	26 (22–24, 33, 35–37, 41, 42, 44–46, 53, 55–57, 59, 61, 62, 68–71, 73, 74, 78)	18	NA	Higher number of prescribed medications	OR 1.06 (95% CI 1.39 to 1.98) p<0.001[57]
			Adjusted for age, sex, number of regular medicines and diagnosed chronic condition	Higher number of prescribed medications	PIM: OR 1.2 (95% CI 1.17 to 1.24) p<0.05 PPO: OR 1.04 (95% CI 1.01 to 1.07) p<0.05[69]
			NA	≥4 medications	OR 1.91 (95% CI 1.83 to 2.0) p<0.001[33]
			NA	Higher number of prescribed medications	OR 1.99 (95% CI 1.80 to 2.18) p=0.000[18]
			Adjusted for age, sex, education level, partnership, per capita income and occupation	≥5 medications	Beers 2003: OR 2.9 (95% CI 2.1 to 3.8) Beers 2012: OR 2.7 (95% CI 2 to 3.6)[29]
			Adjusted for disability, coronary artery disease, heart failure and other comorbidities	≥5 medications	IP: OR 2.9 (95% CI 1.5 to 5.8) Potential major DDI: 3.8 (95% CI 1.7 to 8.2)[37]
			Adjusted for age, sex, number of chronic conditions and number or drug consumed	≥3 medications	OR 3.21 (95% CI 2.78 to 3.59) p<0.001[27]
			Adjusted for age, sex, length of hospital stay and residential situation	≥5 medications	OR 3.22 (95% CI 1.40 to 7.42) p=0.006[32]
			NA	≥6 medications	OR 3.37 (95% CI 2.08 to 5.48) p<0.001[30]
			NA	≥7 medications	OR 4.528 (95% CI 4.52 to 4.54) p<0.001[49]
			Adjusted for age, sex, CCI, history of cardiovascular disorder and history of digestive disorder	≥5 medications	OR 5.4 (95% CI 3 to 9.7) p<0.001[64]
			Adjusted for sex, age and number of chronic drugs	≥6 medications	OR 5.59 (95% CI 5.39 to 5.80)[38]
			NA	≥5 medications	OR 5.69 (95% CI 5.0 to 6.48) p<0.05[52]
			NA	≥6 medications	STOPP: RR 6.837 (95% CI 4.155 to 11.247) START: RR 2.051 (95% CI 1.25 to 3.367)[65]
			NA	≥10 medications	OR 7.33 (95% CI 7.15 to 7.51) p<0.05[40]
			NA	≥9 medications	OR 7.43 (95% CI 3.20 to 17.23) p<0.001[66]
			NA	≥10 medications	Male: OR 8.2 (95% CI 8 to 8.4) Female: OR 9.6 (95% CI 8.2 to 11.2)[42]
			NA	≥10 medications	OR 11.45 (95% CI 11.2 to 11.7) p<0.01[67]

Table 4 Medication errors healthcare professional-related risk factors

Risk factor	Studies with positive association (n)	Controlled studies (n)	Adjusted for	OR or RR or beta (95% or 99% CI) p values
Age ≥51 years	2 (53, 71)	2	NA	OR 1.03 (95% CI 1.01 to 1.06) p<0.01[67]
			NA	OR 1.238 (95% CI 1.235 to 1.242) p<0.001[49]
More than one physician involved in their care	5 (22, 33, 64, 77, 78)	3	NA	Beta 0.7 (95% CI 0.5 to 1.0) p=0.034[73]
			Adjusted for age, sex, number of chronic conditions and number or drug consumed	OR 1.39 (95% CI 1.17 to 1.67) p<0.001[27]
			Adjusted for age and number of prescriber	OR 3.52 (99% CI 3.44 to 3.60)[60]
Male general practitioner	2 (53, 71)	2	NA	OR 1.07 (95% CI 1.05 to 1.10) p<0.01[67]
			NA	OR 1.206 (95% CI 1.202 to 1.210) p<0.001[49]
Frequent changes in prescription	1 (77)	1	NA	Beta 0.4 (95% CI 0.2 to 0.9) p=0.019[73]
Not considering the prescription of other physicians	1 (77)	1	NA	Beta 1.9 (95% CI 1.1 to 3.2) p=0.013[73]
Inconsistency in the information	1 (77)	1	NA	Beta 4.4 (95% CI 1.3 to 14.8) p=0.013[73]
Outpatient clinic visit	1 (46)	1	NA	1.4 (male 95% CI 1.3 to 1.4) (female 95% CI 1.3 to 1.6)[42]
Family medicine/general practice specialty	3 (53, 56, 71)	3	NA	OR 1.06 (95% CI 1.03 to 1.10) p<0.01[67]
			NA	OR 1.267 (95% CI 1.265 to 1.269) p<0.001[49]
			NA	OR 1.46 (95% CI 1.28 to 1.65) p<0.05[52]

CCI, Charlson Comorbidity Index; IP, inappropriate prescribing; NA, not applicable; PIM, potentially inappropriate medication; PPO, potential prescribing omission; START, Screening Tool to Alert doctors to Right Treatment; STOPP, Screening Tool of Older Person's Prescriptions.

Medication-related risk factors

Medication-related risk factors for the development of medication error were multiple medication storage locations used, expired medication present, discontinued medication repeats retained, hoarding of medications, therapeutic duplication,[25] no medication administration routine, poor adherence and patients confused by generic and trade names.[76] In one study by Johnell and Fastbom,[46] multidose drug dispensing users (ie, medicines machine-packed into unit-dose bags for each time of administration) were more exposed to all indicators of potentially inappropriate drug.[46]

Receiving anticoagulant therapy (OR 2.38, 95% CI 2.15 to 2.64) was strongly associated in one study to potential drug–disease interactions.[33]

The use of OTC and/or prescribed drugs was a risk factor in two additional studies.[29 43] The use of OTC medications was associated with PIM; the OR after adjusting for age, sex, education level, partnership, per capita income and occupation was 2.5 (95% CI 1.7 to 3.6) using Beers 2003 and 1.8 (95% CI 1.2 to 2.5) using Beers 2012.[29]

ERROR-RELATED ADVERSE EVENTS

Error-related adverse events or preventable ADEs were mentioned in six studies.[22 28 29 31 32 77] The most frequently reported consequences were ED visits and hospitalisation.

Two methods for detecting ADE were applied: an ADE monitor (ie, using computerised programs composed of rules that identified incidents suggesting that an ADE might be present)[22] and using trigger tools to detect ADEs.[77]

Incidence and/or prevalence

One study estimated preventable ADE incidence as 15/1000 person-years.[22] ACE inhibitors and beta-blockers

were the most common medications associated with preventable ADE.[22] The estimate of the prevalence of preventable ADE was calculated from five studies as detailed below.[28 29 31 32 77]

All stages of medicines' management process

Field *et al* found the prevalence of error caused by patients leading to an adverse event to be 0.38%, that is, less than 1% of the overall population experienced a medication-related adverse event. They found that the majority of patient errors-related adverse events (n=129) occurred in modifying the medication regimen (42%), administering the medication (32%) or not following clinical advice about medication use (22%).[77] The medications associated with more than 10 preventable ADEs were anticoagulants/antiplatelets, cardiovascular drugs, diuretics, hypoglycaemics and non-opioid analgesics.[77]

ERROR-RELATED ADVERSE EVENTS ACCORDING TO MEDICINES' MANAGEMENT PROCESS

Prescribing errors

Drug–drug interaction

Obreli-Neto *et al*[28] found that DDI-related adverse drug reaction (ADR) occurred in 7% of patients. Warfarin, digoxin, spironolactone and acetylsalicylic acid were the drugs most commonly associated with DDI-related ADRs.[28]

Potentially inappropriate medication

Forty-six per cent of participants reported complaints related to ADEs by interview; 95% of these were caused by prescribed medications.[29]

Use of inappropriate drugs was associated with an increased risk of nursing home admission, hospitalisation, more outpatient visit days, ED visits and having ADEs or ADRs.[44 52 63 68]

Other errors

Adverse events (undertreatment due to deletions, ADR due to additions and DDI) related to discrepancy between the medication lists from the patient, the GP or the pharmacy were identified in 24% of patients.[31] Two discrepancies were categorised as having the potential to cause severe patient harm.[32]

RISK FACTORS

Risk factors for the error-related adverse events were discussed in three studies only.[28 31 77]

Patient-related risk factors

Field *et al* found that the number of regularly scheduled medications (seven or more medications) (OR 3.3, 95% CI 1.5 to 7.0) and a Charlson Comorbidity Index (CCI) score of 5 or more (OR 15.0, 95% CI 6.5 to 34.5) were both associated with higher risk of patient error leading to preventable ADE.[77] Obreli-Neto *et al*[28] found that an age of 80 years or more (OR 4.4, 95% CI 3.0 to 6.1, p<0.01), a CCI of 4 or more (OR 1.3, 95% CI 1.1 to 1.8, p<0.01) and consumption of five or more medications (OR 2.7, 95% CI 1.9 to 3.1, p<0.01) were associated with the occurrence of DDI-related ADRs. In addition, Tulner *et al*[31] found that the number of medications was significantly positively correlated with medication discrepancy adverse patient events.

Medication-related risk factors

The use of medication with narrow therapeutic indices such as warfarin was associated with an increased risk of DDI-related ADRs (OR 1.7, 95% CI 1.1 to 1.9, p<0.01).[28]

DISCUSSION

Summary of main findings

We sought to critically review previous studies conducted in the community of the incidence/prevalence of medication errors and associated adverse events and to identify the main risk factors. We identified 60 studies carried out in various countries providing a comprehensive assessment of the available evidence on the epidemiology of medication errors and error-related ADEs in community settings.

No relevant studies on the incidence of medication errors in these settings were found. The reported point or period prevalence of medication errors in community settings had a very wide range (ie, 2%–94%). This wide range appears, at least in part, to be due to the inconsistency in the definitions of the medication errors used in the studies, differences in populations studied, methodologies employed for error detection and different outcome measures. More than half (37 studies) of the resulting studies were regarding the prescription of inappropriate drugs within the prescribing error stage in an elderly age group using different criteria. The comparison of those criteria is challenging due to the difference in medication use, consumption and availability of those medications to patients between countries. Further work is needed to review errors occurring at administration and dispensing stages of the medicines' management process.

As for preventable ADEs, which may in some cases occur as a result of medication errors, only one study reported error-related adverse events incidence, measured as 15/1000 person-years.[22] The prevalence of preventable ADE was further reported in five other studies and varied according to the medication error type that resulted in the adverse event.

The most common patient-related risk factors for both medication errors and preventable ADEs mentioned were the number of medications used by the patient and the increased age of patients.

Strengths and limitations

The main strength of this systematic review is that a rigorous and transparent process has been employed, which included no language restrictions, an independent screening of titles and abstracts, independent data extraction and critical appraisal of included studies by

two reviewers. It is the first review undertaken within community settings. The use of the ICPS conceptual framework,[17] which provides a comprehensive definition of each concept and type of error in the medicines' management process, is a further strength.

However, several limitations need to be considered. First, despite the thorough process, no data were found regarding the dispensing error stage. This might be due to the lack of a 'dispensing error' key term in our search strategy, although 'medication therapy management' as a key term was included. However, 10 studies on dispensing errors were excluded because they failed to satisfy the inclusion criteria on one or more counts. Second, no data were found regarding the administration error stage. However, 14 studies on administration errors were also excluded for the same previous reason. Third, this systematic review had different outcomes reported in a variety of ways using different tools and methodology, which made combining results in one meta-analysis difficult. Lastly, the studies addressed risk factors adjusted for different confounders, which makes it difficult to generate comparable estimates and/or make causal inferences about whether the harm resulted from the medication error.

Comparison of the findings with previous studies

The definitional variation issue is supported by another two reviews.[78 79] Other systematic reviews focusing on the safety of primary care contexts only have identified studies with vastly different prevalence estimates of the rates of medication errors. These reflect differences in definitions, sampling strategy and populations studied; none have investigated the risk factors for medication errors.[80 81]

Implications for research, policy and practice

There is a need for (1) improvement in the quality of research in this area—it is important that all researchers provide a standardised set of outcome measures of medication errors or internationally accepted terminology and definitions of key concepts; (2) training and monitoring of healthcare professionals with the involvement of medication safety pharmacists in the community; (3) empowering and educating the patients and the public, particularly those with chronic diseases and polypharmacy, to increase their knowledge of medication safety with a record of the current medication list for each patient; (4) patient use of tools and technology particularly for monitoring and follow-up; and (5) encourage the reporting of medication errors, administration errors and dispensing errors.[82] This would strengthen the quality of research, improve the development of strategies to detect and prevent these errors, and provide a safer environment for the community to self-care safely.

CONCLUSIONS

We found a very wide variation in the medication error and error-related adverse events rate between studies, which, at least in part, reflects differences in their definitions, methodologies employed for error detection or clinical heterogeneity, that is, differences in populations studied and different outcome measures. Most of the studies were conducted on elderly populations in economically developed countries. There is therefore clearly a need to extend this work to low-income and middle-income countries, particularly give the WHO's recent launch of a Global Medication Safety Challenge.[82 83] Furthermore, most studies focused only on inappropriate prescribing with relatively little attention to other stages such as administration and dispensing. The most common patient and medication-related risk factors for both medication errors and preventable ADEs were the number of medications used by the patient, increased age and receiving anticoagulant therapy. The most common healthcare professional-related risk factor for medication error was when more than one practitioner was involved in the care of patients and care provision by family medicine and GP specialities.

This study has identified important limitations and discrepancies in the methodology used to study medication errors and error-related ADEs in community settings. These findings need to be considered in the context of designing future research related to medication safety. More research is needed in the areas of incidence of medication errors, administration error and dispensing errors and reporting. Researchers should use a more consistent set of definitions and outcomes in order to facilitate collation and synthesis of data.

ETHICS AND DISSEMINATION

The systematic review protocol was published in *BMJ Open* on 31 August 2016 and is registered with PROSPERO, an international prospective register of systematic reviews.[11 12] It is reported using PRISMA. Trial registration number: CRD42016048126.

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Contributors GAA conceived the idea for this review, conducted the systematic literature search, study inclusion, data extraction and quality assessment. NAS participated in the study inclusion, data extraction and quality assessment. MAM participated in data extraction. NA participated in data extraction and quality

assessment. GAA led the writing and drafting of the manuscript, and this was commented on critically by AS, EG, HA and NAS.

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4.3 Chapter summary

The aim of my systematic review was to critically review previous studies conducted in the community of the incidence/prevalence of medication errors and associated adverse events and to identify the main risk factors. We identified 60 studies carried out in various countries providing a comprehensive assessment of the available evidence on the epidemiology of medication errors and error-related ADEs in community settings.

No relevant studies on the incidence of medication errors in these settings were found. The reported point or period prevalence of medication errors in community settings had a very wide range (i.e. 2.0-94.0%). This wide range appears, at least in part, to be due to the inconsistency in the definitions of the medication errors used in the studies, differences in populations studied, methodologies employed for error detection, and different outcome measures. More than half (37 studies) of the resulting medication errors studies were regarding the prescription of inappropriate drugs within the prescribing error stage in an elderly age group using different criteria. The comparison of those criteria is challenging due to the difference in medication use, consumption and availability of those medications to patients between countries. Further work is needed to review errors occurring at administration and dispensing stages of the medicines' management process.

As for preventable ADEs, which may in some cases occur as a result of medication errors, only one study reported error-related adverse events incidence, measured as 15/1000 person-years.(89) The prevalence of preventable ADE was further reported in five other studies and varied according to the medication error type that resulted in the adverse event.

The most common patient-related risk factors for both medication errors and preventable ADEs mentioned were the number of medications used by the patient and the increased age of patients. The most common healthcare professional-related risk factors for medication error was when more than one practitioner was involved in the care of patients and care being provided by family medicine and GP specialities.

Most of the studies were conducted on elderly populations in economically-developed countries. There is therefore clearly a need to extend this work to low- and middle-income countries, particularly given the WHO's recent launch of a Global Patient Safety

Challenge.(90, 91) My systematic review did not find a validated method for detecting all classes of medication errors. Bearing this in mind and the fact that most of the preventable ADEs are as a result of prescribing errors and/or medication monitoring errors,(92) Avery et al. (2012), in the Pharmacist-led information technology-based intervention to reduce rates of clinically important errors in primary care (PINCER) trial for medication errors in the UK, developed a list of clinically important errors in prescribing and monitoring in primary care. The feasibility of doing a pilot retrospective cohort study (Phase 2), based on the baseline method developed in the PINCER trial (85), will be explained in the following chapter.

Chapter Five: Phase 2: Feasibility Study to Inform the Development of a Pilot Retrospective Cohort Study Investigating the Epidemiology of Medication Errors in Adults Using Electronic Health Records in Riyadh, Saudi Arabia

5.1 Introduction

In Phase 1, the systematic literature review identified 60 different original studies looking at medication errors, of which only six measured ADEs as an outcome. In the earliest study identified, Field (2007) used EHRs for detecting ADEs through computer generated signals of possible drug-related incidents and then identified the events related to patient medication errors.(93) Gandhi (2010) used ADE monitoring triggers (or rules) that were programmed and then run against data in the EHR to detect ADEs.(89) The other four studies looked at ADEs resulting from discrepancies (between the medications described by the patients and caregivers with the drugs listed by their GP), drug-drug interaction- related adverse drug reaction (DDI-related ADR) and the use of potentially inappropriate medicine (PIM). (94-97)

My systematic review revealed that identification of ADEs could most efficiently be carried out by using either computer-generated signals of possible drug-related incidents or trigger tools based on abnormal laboratory values and prescriptions for antidotes.(89, 93) Identifying signals included elevated drug levels, abnormal laboratory results, the use of medications considered to be antidotes, and diagnoses that could reflect an ADE. Computer-generated signals or trigger tools have been used to study ADEs (ADEs; ADR and medication errors that cause harm). However, the use of these two tools has several limitations. For example, they may not detect whether the reported errors were directly related to the medications or to the disease itself; they may require an intensive chart review and may be prone to subjective interpretation.

Previous work has been done on prescribing indicators in general practice, which have been defined as "*statements describing prescribing events that put the patient at risk of harm*" used to monitor prescribing patterns.(98, 99) Investigating prescribing patterns and quality is not included in the aims or objectives of my thesis.

According to the literature review, several methods can be applied to measure and identify the incidence and prevalence of medication errors in the community context. There is no single

approach that is considered to be a gold standard for medication errors detection. Detection of medication errors depends on the setting, the expected type of medication error and the cost of detection.(100)

The provisional plan for the method of this PhD research was to carry out a prospective cohort study, using a telephone survey adapted from Gandhi et al. study,(23) in adults from a randomly selected sample of the community pharmacies within the five regions of the Riyadh city, Saudi Arabia. However, after the completion of Phase 1 and considering the available time and resources, I modified my plans. The systematic review did not identify a validated method for detecting all classes of medication errors. According to the systematic review and previous work, most of the preventable ADEs occur as a result of prescribing and/or medication monitoring errors.(88, 92)

Following discussion with other researchers, I identified a validated tool for measuring medication errors developed by Avery et al. (2012) in the PINCER trial in the UK. The PINCER trial is one of the world's first randomised studies aiming to reduce the risk of medication errors in general practices, which focused on a pre-specified list of clinically important errors in prescribing and monitoring.(85) This list was developed through a series of steps involving a systematic review of the literature, and epidemiological, consensus exercise and pilot work.(92, 101, 102) This present research investigates the epidemiology of clinically important errors in medicine management as defined by the PINCER trial.(85) Hence, I used a method which has been established by previous research in the current context.(85) In order to investigate the relevant outcome measures in a future retrospective cohort study, I first established the feasibility and reliability of using data extraction from the EHRs of KFSH&RC Family Medicine and Polyclinics, Riyadh, SA. Choosing EHR screening for this feasibility and pilot study was the most compatible option to fit with the imposition set by the Saudi Cultural Bureau, which specified a maximum of three months for a postgraduate student to undertake data collection or fieldwork. Furthermore, the interest is the epidemiology of clinically important errors in medicine management, rather than the adverse events themselves, so Phases 2, 3 and 4 of my research focused only on the medication errors.

Given the global dearth of studies looking at medication errors in the community, the transition across the world from secondary and tertiary care to community-based care, particularly in SA, as well as the absence of studies carried out in the kingdom, this work was both important and timely.

In Phase 2, the feasibility study, I sought to; a) identify the ambulatory setting and electronic database; b) evaluate the feasibility of data extraction and data collection from EHRs; c) check the availability and assess the reliability of key outcome measures; and d) inform the development of Phase 3, a pilot retrospective cohort study that focused on assessing the feasibility of doing a larger Phase 4 study, based on the baseline method developed in the PINCER trial by Avery et al. (2012).(85)
It should be noted that Phase 1 of this research focused on both medication errors and error-related ADEs, but Phases 2, 3 and 4 focused solely on medication errors.

5.2 Methods

A feasibility study is an initial part of a research done before the main study to answer the question 'Can this study work?'. The National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordination Centre has helpfully explained the rationale for a feasibility study stating that it "*focuses on conducting research to examine whether the study can be done*". Thus, feasibility studies are conducted first, followed by pilot studies.(103)

A feasibility study focuses on the process and its rationale is to a) identify the ambulatory setting and electronic database, b) check the procedure of recruitment, c) assess the data collection procedure, d) know sample's characteristics, e) check the availability of outcome measures, and f) evaluate the ability to implement the study.(103)

5.2.1 Setting and electronic database

I tried to identify a potential healthcare setting in which there was access to longitudinal EHR data. To choose the setting of the fieldwork, five ambulatory care centres in Riyadh, SA, were contacted by Email communications and phone calls, namely:

1. KFSH&RC Family Medicine and Polyclinics Centre. There were several reasons for carrying out this study at KFSH&RC. Firstly, usually, patients choose to receive healthcare from KFSH&RC because of the high-quality care provided. Secondly, greater populations were covered by this hospital compared to the following four settings, which allowed a more complete and accurate picture of medication error

rates. The centre serves a population of 35,000 Saudi and non-Saudi employees and their dependents of all ages. It has a well-developed electronic system Integrated Clinical Information System (ICIS), which includes reporting of medication errors. In 2015, the Family Medicine provision has been awarded Healthcare Information and Management Systems Society (HIMSS) 7 accreditation. The KFSH&RC Family Medicine-Riyadh city, SA became the first ambulatory care service outside the USA to achieve HIMSS 7 status.(104) Several meetings and discussions were conducted with Dr Abdullah Alkenizan (AK) from KFSH&RC regarding the collaboration work, the applicability of the method and ethical considerations.

2. King Khalid University Hospital ambulatory care, this setting was subsequently discarded as it had a new electronic System for Integrated Health Information (eSiHi) launched only in May 2015 and thus the potential for having missing data and inaccurate coding was high.
3. NGHA, this setting was not considered suitable as the institution is specifically for employees of this governmental body, together with their families and dependents.
4. Prince Sultan Military Medical City, this setting was not considered suitable for the same reason of the NGHA setting and it did not have an EHR system for ambulatory care.
5. Security Forces Hospital, this setting was not considered suitable for the same reason of the NGHA setting.

KFSH&RC, located in the capital of SA, Riyadh, is a 1086-bed tertiary care facility that provides the highest level of specialised healthcare in an integrated educational and research setting. The Department of Family Medicine and Polyclinics is comprised of two sections, namely Family Medicine and Polyclinics. *"The Section of Family Medicine is responsible for the healthcare needs of hospital employees and their eligible dependents of all age groups (approximately 35,000). Family Medicine provides services that include screening, diagnosis, management and prevention of physical and psychosocial conditions, as well as providing health education and medical counselling, occupational and infection control services including assessment of pre-employment, needle stick injuries and tuberculosis (TB) surveillance. The Section of Polyclinics serves as an initial assessment and referral clinic to determine a patient's eligibility for tertiary care services at KFSH. It is also an ambulatory care facility for tertiary care patients who need special additional management of their*

chronic diseases. In addition, Polyclinics provides back up support to the Emergency Room for cases, which need urgent follow-up. Polyclinics are comprised of Medical, Pediatrics and Orthopedic Clinic".(105)

5.2.2 Methods

Inclusion/exclusion criteria:

Patients' records were considered eligible if they were for adults of 18 years and over, recorded to be receiving at least one prescribed/OTC medication and had been registered with the Family Medicine and Polyclinic department for at least 15 months prior to data extraction. The 15 months retrospective duration was chosen as that period was specified in the QRESEARCH outcomes.(85) Records were excluded if they related to patients who were under 18 years, had no medications recorded at any point in time over the study period, if their outcome measures occurred during hospitalisation or ED visits, or if they were lost to follow-up; specifically, if the patient had not attended the clinic, had left the clinic or had died.

Sampling:

For sampling in the feasibility phase, I used a systematic random sample from each KFSH&RC Family Medicine clinic during the period from 14 May 2017 to 18 May 2017. Systematic sampling is "*The procedure of selecting according to some simple, systematic rule, such as all persons whose names begin with specified alphabetic letters, born on certain dates, or located at specified points on a master list*".(106) The reason for choosing a systematic random sample in this phase was because it was convenient, and sampling was undertaken before I had received the ICIS training.

Outcome measures:

Patients records were then reviewed to obtain one positive outcome measure (medication error) of each of the outcome measures listed (Box 5-1). For the outcome measures: a) the numerator of each of the outcome measures listed in **Error! Reference source not found.** is considered positive if the patient had a potential medication error; and b) the denominator of each of the outcome measures listed is considered positive if the patients had a potential risk

of medication error. The maximum number of patients reviewed in the feasibility phase considering the time period was 500. If some outcome measures had not been observed after 500 records had been reviewed, such outcome measures were classed as 'rare' and were considered for exclusion from the pilot and cohort study phases.

5.2.3 Training on the ICIS

I received training on the ICIS and I was able to ask specific questions that helped in data collection e.g. how to develop a list of patients visiting the Family Medicine and Polyclinics in a specific period. No training was needed for the secondary data extractor Salma Al-khani (SK) as she worked in KFSH&RC and she was familiar with the system.

5.2.4 Availability and reliability of key outcome measures

The outcome measures used in the feasibility study consisted, initially, of three primary outcomes, seven secondary outcomes and an additional two composite secondary outcome measures, taken from the original PINCER trial.(85) In addition, another nine outcome measures were taken from the revised updated PINCER outcomes.(107) See Box 5-1. In a study by Spencer (2014) that aimed to identify and update a set of prescribing indicators for assessing the safety of prescribing in general practice, it was considered by a panel of healthcare professionals that 13 of these indicators were associated with high risk and three with extreme risk to patients.(99) The medicines' management processes involved in these outcomes were prescribing (contraindication and dosing error) and monitoring errors. Details of each error stage, ADEs and risk are given in Appendix 7. In this phase, the availability of the necessary data and outcome measures were sought.

A working definition of reliability was that "*a measurement is reliable when it is stable; i.e. when repetition of an experiment or measurement gives the same results*".(106)

Primary outcomes

1. Patients with a history of peptic ulcer who have been prescribed a non-selective non-steroidal anti-inflammatory drug (NSAID) without co-prescription of a proton-pump inhibitor (PPI)
2. (2a) Patients with asthma who have been prescribed a beta-blocker (β-blocker)

3. Patients aged 75 years and older who have been prescribed an angiotensin converting enzyme (ACE) inhibitor or a loop diuretic long-term who have not had a computer-recorded check of their renal function and electrolytes in the previous 15 months

Secondary outcomes

(2b) Patients with asthma [and no history of coronary heart disease (CHD)] who had been prescribed a β-blocker

4. Proportion of women with a past medical history of venous or arterial thrombosis who had been prescribed the combined oral contraceptive pill
5. Patients receiving methotrexate for at least 3 months who had not had a full blood count recorded (5a) or liver function test (5b) in the previous 3 months
6. Patients receiving warfarin for at least 3 months who had not had a recorded check of their International Normalised Ratio (INR) in the previous 12 weeks
7. Patients receiving lithium for at least 3 months who had not had a recorded check of their lithium concentrations in the previous 3 months
8. Patients receiving amiodarone for at least 6 months who had not had a thyroid function test in the previous 6 months
9. Patients receiving prescriptions of methotrexate without instructions that the drug should be taken every week
10. Patients receiving prescriptions of amiodarone for at least 1 month who are receiving a dose of more than 200 mg per day

Composite secondary outcome measures

11. Patients with at least one prescription problem (a combination of outcome measures 1, 2, or 4)
12. Patients with at least one monitoring problem (a combination of outcome measures 3, 5, 6, 7, or 8)

Additional revised updated outcome measures

13. Prescription of an oral NSAID, without co-prescription of an ulcer-healing drug, to a patient aged ≥ 65 years
14. Prescription of an anti-platelet drug, without co-prescription of an ulcer-healing drug, to a patient with a history of peptic ulceration
15. Prescription of warfarin or New Oral Anti-Coagulant (NOAC) in combination with an oral NSAID

16. Prescription of warfarin or NOAC and an anti-platelet drug in combination without co-prescription of an ulcer-healing drug
17. Prescription of aspirin in combination with another anti-platelet drug without co-prescription of an ulcer-healing drug
18. Prescription of a long-acting beta-2 agonist inhaler (excluding combination products with inhaled corticosteroid) to a patient with asthma who is not also prescribed an inhaled corticosteroid
19. Prescription of an oral NSAID to a patient with heart failure
20. Prescription of antipsychotics for >6 weeks in a patient aged ≥ 65 years with dementia but not psychosis
21. Prescription of an oral NSAID to a patient with estimated Glomerular Filtration Rate (eGFR) < 45

Box 5-1. Outcome measures from the PINCER trial and the revised updated PINCER outcomes.(85, 107)

5.2.5 Feasibility and practicability of data extraction and data collection from EHRs

The transition from paper medical files to EHR systems has facilitated the development of electronically extracted data from the EHRs, which may be perceived as large health information databases. These databases, therefore, can serve as clinical research resources. The researcher must be able to demonstrate that the electronically extracted data are of sufficient quality.(108) Because of the lack of technical capacity to ensure accuracy and quality, and to avoid the delay that would be necessary for generating the required anonymised data electronically from the electronic medical records department in KFSH&RC, collecting data from the EHRs was undertaken manually by reviewing individual EHR. This method of data collection is distinct from the data extraction approach in the PINCER trial, (84, 85) which was undertaken electronically. A paper-based data collection form was developed for the feasibility study (See Appendix 10). For validity "*An expression of the degree to which a measurement measures what it purports to measure*",(106) the data collection form was double-checked independently by the Salma Al-khani (SK).

5.2.6 Ethics

According to the KFSH&RC guidelines and the policy of the research ethics committee (REC), the retrospective chart review method did not require a subject's consent and KFSH&RC may waive that consent (see Section 6.2.9).(109) I submitted the research protocol to KFSH&RC on 28 March 2017. The research protocol, data collection sheet and waiver of informed consent (in place of an individual's informed consent) were approved by the REC in KFSH&RC, Riyadh, SA (project # 2171 060) (Appendix 9). The confidentiality of the data was maintained by giving each EHR a code number to preserve patient privacy, I did not record any patient identifier information e.g. (names, addresses and medical record number) that could be used to link data to participants.

After the research approval was obtained, I had access to the ICIS as the research coordinator and a secondary data extractor (SK), had access to ICIS because she is an employee of KFSH&RC.

5.3 Results

Of the five ambulatory settings reviewed, the EHR database at KFSH&RC was selected on the grounds that it was possible to: access longitudinal EHR data; construct a suitable sampling frame; and extract relevant outcome variables.

An average of 200 patients were seen daily by physicians in the Family Medicine and Polyclinics. I retrospectively reviewed a total of 500 records fulfilling the inclusion criteria from 01 February 2016 to 31 May 2017 (15 months prior to data extraction).

Analysis to achieve objectives

5.3.1 Availability of necessary data in the EHR

All the necessary information from each patient's EHR was available in one system (ICIS), including baseline characteristics, medications, diagnosis using coding of the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10),(110) together with laboratory results, including urea and electrolytes, blood count, liver function, INR, thyroid function, drug level and surgical pathology report for biopsy to detect peptic ulcer. In detail, the following variables were available:

- All the patients' visits to Family Medicine and Polyclinics could be seen under *document viewing,* along with the visiting dates.
- Diagnosis could be seen in *Problems and diagnosis,* and under *document viewing,* as well as in the indication of each prescribed medication.
- The medication was noted under the *medication list*.
- All laboratory results, with their dates, were recorded in the *flowsheet* with specifying the study duration i.e. before 15 months or more.

The availability of drugs under the following drug classes in KFSH&RC were sought through reviewing the KFSH&RC formulary: ACE inhibitors, anti-platelets, antipsychotics, β-blockers, gastro-protective agents, long-acting beta-2 agonist inhaler, loop diuretics, NOACs, NSAIDs and oral contraceptives. Details of the medications available under each class are shown in Table 5-1.

Class	Drug generic name	Restricted drug (specialty other than Family Medicine physician can prescribe the drug)
Antipsychotic agent	ChlorproMAZINE OLANZapine- Family Medicine physicians are authorised to renew prescriptions of olanzapine. RisperiDONE- Family Medicine physicians are authorised to renew prescriptions of risperidone. Trifluoperazine	ARIPiprazole- Prescribing restricted to psychiatrists. CloZAPine- Prescribing restricted to psychiatry and neurology consultants. OLANZapine- Prescribing oral form restricted to psychiatrists, neurologists for treatment of schizophrenia and bipolar mania, Family Medicine physicians are authorised to renew prescriptions of olanzapine. Pimozide- Prescribing restricted to neurologists for the treatment of Tourette's disorder and psychiatrists for schizophrenia. Haloperidol- Adult haematology/oncology for management of chemotherapy-associated nausea or vomiting. RisperiDONE- Prescribing oral form restricted to psychiatrists

		and neurologists for use as a second-line agent for patients who do not respond to, or are intolerant to, traditional neuroleptics. QUEtiapine- Prescribing restricted to psychiatrists, neurologists and adult intensive care unit (ICU) physicians. Ziprasidone- Prescribing restricted to psychiatrists.
NOAC		Rivaroxaban- Prescribing restricted to the approved indications as per guidelines. Argatroban- Prescribing restricted to haematology consultants for patient with Heparin induced thrombocytopenia (HIT). Adult ICU consultants and cardiac ICU consultants may initiate therapy for 24 hours until a hematology consultation is obtained. Subsequent doses require haematology approval. Fondaparinux- Prescribing restricted to adult cardiology physicians and adult haematology/thromboembolism services according to guidelines.
Oral anticoagulant	Warfarin	

Oral Anti-platelet	Aspirin Clopidogre Dipyridamole (oral)	Dipyridamole- Prescribing injection form restricted to cardiologists. Ticagrelor- Prescribing restricted to adult cardiology and emergency physicians.
NSAID	Aspirin Diclofenac Ibuprofen Indomethacin Meloxicam Naproxen Sulindac	
Non-selective β-blocker, beta 1 selective	Atenolol Betaxolol	

	Esmolol Metoprolol	
Non-selective β-blocker	Dorzolamide and Timolol Timolol Propranolol Sotalol [FR]- Family Medicine and Internal Medicine Consultants may prescribe sotalol for maintenance therapy.	Sotalol [FR]- Prescribing restricted to cardiologists and adult intensivists for initiation of therapy.
Long Acting Beta 2 Agonist	Budesonide and Formoterol Fluticasone and Salmeterol	
Long Acting Beta 2 Agonist excluding combination products with inhaled corticosteroid	Salmeterol	
Combined oral contraceptive	Diane®-35 | Cyproterone 2 mg | Ethinyl estradiol 35	

	21 tabs		mcg
	Logynon® 6 tabs 5 tabs 10 tabs	Levonorgestrel 0.05 mg Levonorgestrel 0.075 mg Levonorgestrel 0.125	Ethinyl estradiol 30 mcg Ethinyl estradiol 40 mcg Ethinyl estradiol 30 mcg
	Marvelon® 21 tabs	Desogestrel 0.15 mg	Ethinyl estradiol 30 mcg
	Microgynon®-30 21 tabs	Levonorgestrel 0.15 mg	Ethinyl estradiol 30 mcg

<table>
<tr><td></td><td><table>
<tr><td>Micronor®
28 tabs</td><td>Norethindrone 0.35 mg</td><td>None</td></tr>
<tr><td>Norinyl®-1
21 tabs</td><td>Norethindrone 1 mg</td><td>Mestranol 50 mcg</td></tr>
</table>KFSH uses lower potency estrogen component oral contraceptives. Norethisterone = norethindrone</td><td></td></tr>
<tr><td>ACE inhibitor</td><td>Captopril

Enalapril

Lisinopril</td><td></td></tr>
<tr><td>Loop diuretics</td><td>Furosemide</td><td></td></tr>
<tr><td>Gastro-protective PPI</td><td></td><td>Esomeprazole [FR] - Prescribing restricted to adult gastroenterology consultants for the treatment of 50 patients per year only.

Omeprazole [FR] - Prescribing intravenous form restricted to</td></tr>
</table>

		emergency medicine physicians, intensivists and gastroenterologists.
Gastro-protective Cytoprotective agents		Misoprostol - Prescribing restricted to obstetrics and gynaecology and gastroenterology physicians.
Gastro-protective H2 receptor antagonist	Ranitidine (double dose)	
Dementia drugs	Donepezil Memantine	Rivastigmine – prescribing restricted to neurologists and psychiatrists.
	Methotrexate (oral)	Methotrexate -Prescribing Ebetrexate® prefilled syringe restricted to adult and pediatric rheumatologists for treatment of juvenile and adult rheumatoid arthritis for outpatient use only.
	Lithium	
	Amiodarone-Oral tablets are not restricted.	Amiodarone- Prescribing injectable amiodarone restricted to cardiologists and intensivists.

Table 5-1. Medications available in the KFSH&RC and their restrictions.

Descriptive analysis:

All the outcomes were identified at least once after reviewing 500 records in the feasibility phase apart from the following three outcomes:

- Outcome 7: patients receiving lithium for at least three months who had not had a recorded check of their lithium concentrations in the previous three months
- Outcome 8: patients receiving amiodarone for at least six months who had not had a thyroid function test in the previous six months
- Outcome 10: patients receiving prescriptions of amiodarone for at least one month who were receiving a dose of more than 200 mg per day.

The following single outcome was not seen as an error in this phase:

Outcome 9: Patients receiving prescriptions of methotrexate without instructions that the drug should be taken every week.

The instruction for taking methotrexate every week is specified on the medication label as (every seven days).

5.3.2 Feasibility and practicability of data extraction and data collection from EHRs

The data collection form was tested and reviewed on 10 electronic records. It was also double-checked independently by the secondary data extractor (SK) (See Appendix 10).

5.4 Chapter summary

This phase of work was designed to identify the ambulatory setting and electronic database and to assess the feasibility of using EHRs to conduct epidemiological research on a pre-specified list of clinically important errors in medicine management (Box 5-1). I selected the EHRs of KFSH&RC Family Medicine and Polyclinics, Riyadh, SA. All the outcomes were seen at least once in a total of 500 patients, apart from Outcomes 7, 8, 9 and 10 for amiodarone, methotrexate and lithium. However, none of the outcome measures were excluded from the pilot phase (Phase 3), because it was considered possible that Outcomes 7, 8 and 10 could appear when screening a higher number of records.

The following three points were confirmed in this feasibility phase: the secondary data extractor and I were able to access the EHRs, I could construct the sampling framework for the pilot study through simple random sampling, and all outcome measures were identified

apart from four outcomes for amiodarone, methotrexate and lithium (as detailed above) and they could all be used in the following phases.

The findings from this phase of my research suggested that the pilot phase is feasible, likely to provide random sample and all information needed for the outcome measures was available in the one system. I concluded that I could proceed to Phase 3 without excluding any of the outcome measures.

Chapter Six: Phase 3: A pilot Retrospective Cohort Study Investigating the Epidemiology of Medication Errors in Adults Using Electronic Health Records in Riyadh, Saudi Arabia

6.1 Introduction

Phase 2 of this study was initiated to identify and select the ambulatory setting and electronic database and to test the feasibility of using data from EHRs of KFSH&RC Family Medicine and Polyclinics, Riyadh, SA. The findings from Phase 2 indicated that the pilot phase would be feasible. The reason for undertaking this pilot retrospective cohort study was to inform sample size calculations and to inform plans for undertaking a larger retrospective cohort study, based on the methods developed for baseline assessments in the PINCER trial.(85) Given the limited research team and time period for this PhD, Phases 3 and 4 focused only on medication errors, which was in contrast to the systematic review (Chapter 4) in which I focused on both medication errors and error-related ADEs.

The research design, sampling, variables, data collection, statistical analysis and results of the pilot study are discussed in this chapter along with a discussion of changes to methods that were carried forward into the main study (Chapter 7).

6.2 Methods

A pilot study is *"A small-scale test of the methods and procedures to be used on a larger scale if the pilot study demonstrates that these methods and procedures can work*"(106) and is often used by researchers to pre-test a research instrument and/or approach (Baker, 1994).(111)

A random sample of patients visiting the Family Medicine and Polyclinics in KFSH&RC was selected. Patients using this service would be managing their medication through the outpatient clinic and using medication by themselves and/or with the assistance of a caregiver at home. A retrospective cohort was constructed and patients records were then manually reviewed. Manual data collection was carried out to avoid the delay that would be necessary for generating the required anonymised large number of data electronically from the electronic medical records department at KFSH&RC and because of the lack of informaticians available to provide the data in my timeframe.

6.2.1 Study design

The pilot study sought to build on the feasibility study by providing a clearer focus on outcomes, rather than processes.(103) Conducting a pilot study prior to the main study should enhance the success of the main study and help to identify and resolve any potential sources of problems in the main study.

The pilot retrospective cohort study was designed to measure period prevalence of the primary, secondary, composite secondary and revised updated outcome measures and risk factors. Period prevalence was defined as "*the proportion of individuals with the condition at any time during a specified time period or interval"*.(106)

6.2.2 Participants and sampling

Subjects were selected from the Family Medicine and Polyclinics at KFSH&RC. Sampling was undertaken over one month in 2017; the follow-up was carried out retrospectively, over the 15 months prior to the data extraction from 01 February 2016 to 31 May 2017. The pilot study flowchart (Figure 6-1) provides a description of the population and sample included.

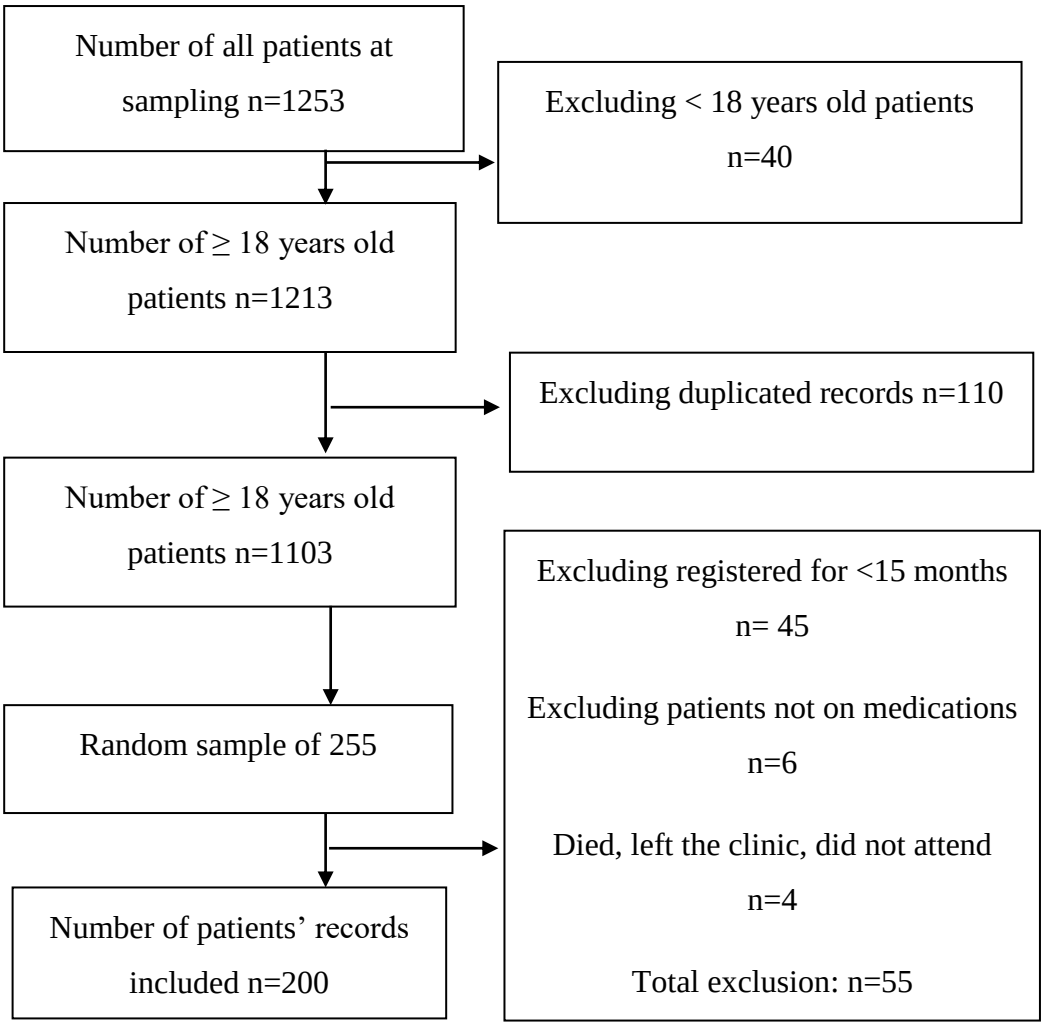

Figure 6-1. Pilot study flowchart outlining population and sample enrolment.

Inclusion criteria:

1. Saudi and non-Saudi adults aged 18 years or over.
2. Patients recorded to be receiving at least one prescribed/OTC medication. These medications were checked against the SFDA list of human medications and were subsequently classified into prescription or OTC medications.(112)
3. Patients who had been registered with the Family Medicine and Polyclinics at KFSH&RC for at least 15 months prior to data extraction.

Exclusion criteria:

1. Patient aged less than 18 years.
2. Patients with an absence of recorded medications at any point in time over the study period.

3. Patients whose primary and secondary outcomes occurred during hospitalisation or ED visits.
4. Those lost to follow-up due to not attending the Family Medicine and Polyclinics appointment, having left the clinic or having died.

Method of sampling:

After attending the training course on the ICIS system, I was able to generate a list of patients visiting the Family Medicine and Polyclinics and to perform sampling. Simple random sampling was chosen to reduce selection bias. Simple random sampling is one type of probability or random sampling in which "*each person has an equal chance of being selected out of the entire population*".(106) A list of all patients who visited the Family Medicine department two weeks before data collection (31 May 2017) was generated. Two weeks was specified because the maximum duration that could be specified by the ICIS for generating a patient list was two weeks, which yielded around 1,500 records. Each person was assigned a number. I excluded paediatric patients. Then, numbers were selected at random, from a table of random numbers, until the desired sample size was attained.(106)

Electronic records were randomly selected using a random number table generated via the 'simple random sample without replacement' function in STATA (version 14) to avoid including the same patient twice.

6.2.3 Variables

Baseline characteristics:

The baseline characteristic variables recorded were age, gender, nationality (Saudi, non-Saudi), diagnosis or underlying conditions and OTC recorded at any point during the 15 months, and polypharmacy (taking five or more medications at any point during the 15 months).

Exposures:

1. Prescribed medications and/or OTC drugs.
2. Risk factors. For more information see Section 6.2.4.

Outcome variables:

1. Period prevalence of the primary, secondary, composite secondary and revised updated outcome measures.

For the primary, secondary, composite secondary and revised updated outcome measures see Box 5-1.(85, 107)

6.2.4 Data sources/measurement

Identification of outcomes

After selecting a random sample from the Family Medicine and Polyclinics, the secondary data extractor (SK) and I undertook in-depth screening of EHRs (i.e. assessing diagnosis, medication list and laboratory data fields). This screening was done in order to investigate the period prevalence of clinically important errors, and risk factors associated with patients at risk of clinically important errors in medicine management (age, gender, nationality, ≥5 regularly scheduled medications and using OTC). The presence, or absence, of the primary, secondary, composite secondary and revised updated outcome measures (the numerator) and the denominator for each outcome measures were recorded. During the EHR review, we focused on the outcomes detailed in Box 5-1. This method was taken from the baseline method developed in the PINCER trial by Avery et al. (2012).(85, 107)

To identify factors predicting patients who would be at risk of experiencing errors during the follow-up period, I conducted a binary logistic regression analysis. The literature suggests that increased age, female gender, using ≥ 5 concurrent medications (polypharmacy) and using OTC medications, may be associated with medication errors.(113) Therefore, my model incorporated the following independent variables: a) age, b) gender, c) nationality, d) ≥5 regularly scheduled medications and e) using OTC. Information including age, gender, nationality, regularly scheduled medications and diagnosis was abstracted from EHRs.

Development of a data collection tool:

Manual data extraction from the EHRs was independently undertaken by two extractors (GA and SK) to minimise the risk of errors in data extraction. A paper-based data collection form was used to complete an extensive summary description of all relative information available in the EHRs to gather the patient's demographics and outcome measures (see Appendix 10).

Any discrepancy or disagreement was checked by me and discussed/resolved by independent double-checking the records or through arbitration by a third reviewer (AK) if a decision could not be reached. This approach was adopted because inter-rater reliability requires completely independent rating of the same event by two or more raters.(114, 115)

The paper data collection forms were stored in a secure location in the clinic (i.e. locked office).
The information in the paper-based data collection tool was transferred to an electronic data sheet using an Excel spreadsheet for the analysis. The electronic data sheet was stored in a password-protected computer and no patient identifying information was recorded.

6.2.5 Bias

Bias is the "*systematic deviation of results or inferences from truth*".(106)

Bias in sampling method:
To reduce the risk of selection bias in sampling, simple random sampling was employed.

Bias in study design:
Selection and information bias are particular problems with retrospective cohort studies where exposure and outcomes have already occurred at the time of subject enrolment.(116) This type of bias cannot be avoided when employing a retrospective study design. Documentation bias may occur within a retrospective review because the investigator must rely on information provided only in the electronic records to identify or assess the outcome.

6.2.6 Study size

A sample size of 10% or more of the major study size is commonly deemed adequate for a pilot study,(117) so up to 200 patient records were required in the pilot study. Related variables and outcomes were extracted by the two data extractors from the 200 randomly selected records.

The original intention was to identify the sample size required to detect the period prevalence and the lowest strength of association odds ratio (OR) between risk factors and outcomes of interest. However, because of the large number of variables and the lack of informaticians available to provide the data in my timeframe that resulted me in choosing the manual method for data extraction, each record needs a maximum of 15 minutes to scan and extract data. Therefore, the largest sample size that was feasible considering the time available, resources and research team size was 2000 records.

6.2.7 Data access and cleaning methods

The electronic data sheet was checked for errors in data entry, outliers and missing data.

For each of the outcome measures, a number of data checks were used to ensure that:(84)

- The ages of the included patients fulfilled the criteria for being included in the relevant outcome measure.
- The drugs fulfilled the criteria for the relevant outcome measure.
- Cases labelled as numerators fulfilled the criteria for being numerators.
- Cases labelled as non-numerators were correctly labelled as non-numerators, whilst also fulfilling the criteria for being denominators.

For monitoring outcome measures, a number of data checks were used to help ensure that:

- The dates of the latest relevant monitoring codes (where available) were used correctly to assign the patient to being either a numerator or denominator.
- In relation to the combined hormonal contraceptive outcome measure (Outcome 4), all patients were female.
- In relation to the methotrexate dosing instructions outcome measure (Outcome 9), only those patients that had dosing instructions recorded were included (i.e. records with blank dosage instructions fields were excluded).

For composite Outcome measure 11:

- Data from Outcomes 1, 2 and 4 (see Box 5-1) were combined, ensuring that they were not double counted, thus identifying patients who appeared one or more times as numerators in order to calculate the proportion of patients with one or more prescribing problems

from those at risk of one or more prescribing problems*. For example, if a patient appeared as a numerator in any of Outcomes 1, 2 and 4, they would appear as a numerator in the composite outcome measure.

*Patients at risk were patients with a positive denominator for Outcomes 1, 2 and 4.

For composite Outcome measure 12:

- Data from Outcomes 3, 5, 6, 7 and 8 (see Box 5-1) were combined, ensuring that they were not double counted, thus identifying patients who appeared one or more times as numerators in order to calculate the proportion of patients with one or more monitoring problems from those at risk of one or more monitoring problems*.(84)

  * Patients at risk were patients with a positive denominator for Outcomes 3, 5, 6, 7 and 8.

An inventory of medical record numbers and patients' code number was used to ensure patients were not included in the dataset more than once.

6.2.8 Statistical methods

Period prevalence calculations:

Microsoft Excel and STATA (version 14) were used to manage and analyse the data.
The overall period prevalence of patients with at least one medication error was calculated as: the number of patients experiencing one or more medication error at any time during the 15 month period (numerator)/the total number of patients in the study population (denominator).(118)
The overall period prevalence of medication errors was calculated as: the number of medication errors at any time during the 15 month period (numerator)/the total number of patients in the study population (denominator).

The prevalence of each primary and secondary outcome measure listed below was described using numerators, denominators and percentages, at patient level.

Primary outcome measures:

- Patients with a history of peptic ulcer prescribed an NSAID (excluding aspirin) without a PPI (numerator)/ Patients with a history of peptic ulcer without a PPI (denominator)
- Patients with asthma prescribed a β-blocker (numerator)/Patients with asthma (denominator)
- Patients aged ≥75 on long term ACE inhibitors or diuretics without urea and electrolyte monitoring in the previous 15 months (numerator)/Patients aged ≥75 on long term (15 months) ACE inhibitors or loop diuretics (denominator).

Secondary outcome measures:

- Patients with asthma and not CHD who are prescribed a β-blocker (numerator)/Patients with asthma and not CHD (denominator)
- Female patients with a history of venous or arterial thromboembolism and arterial thrombosis prescribed combined oral contraceptives (numerator)/Female patients with a history of venous or arterial thromboembolism and arterial thrombosis (denominator)
- Patients prescribed methotrexate for ≥three months without a full blood count in the last three months (numerator)/Patients prescribed methotrexate for ≥ three months (denominator)
- Patients prescribed methotrexate for ≥ three months without a liver function test in the last three months (numerator) / Patients prescribed methotrexate for ≥ three months (denominator)
- Patients prescribed warfarin for ≥ three months without an INR in the last three months (numerator) /Patients prescribed warfarin for ≥ three months (denominator)
- Patients prescribed lithium for ≥ three months without a lithium level in last three months (numerator) / Patients prescribed lithium for ≥ three months (denominator)
- Patients prescribed amiodarone for ≥ six months without a thyroid function test in the last six months (numerator) / Patients prescribed amiodarone for ≥ six months (denominator)
- Patients prescribed methotrexate without instructions to take weekly (numerator) / Patients prescribed methotrexate (denominator)
- Patients prescribed amiodarone for ≥ one month at a dose >200 mg/day (numerator) / Patients prescribed amiodarone for ≥ one month (denominator).

Composite outcome measures:

- Number of patients with at least one prescribing problem (numerator) / Number of patients at risk of at least one prescribing problem (denominator)
- Number of patients with at least one monitoring problem (numerator) / Number of patients at risk of at least one monitoring problem (denominator).

Revised updated outcome measures:(107)

- Patients aged ≥ 65 years prescribed an oral NSAID (excluding aspirin) without co-prescription of an ulcer-healing drug (numerator) /Patients aged ≥ 65 years without co-prescription of an ulcer-healing drug (denominator)
- Patients aged ≥ 18 years with a history of peptic ulceration prescribed an anti-platelet drug without co-prescription of an ulcer-healing drug (numerator) /Patients aged ≥ 18 years with a history of peptic ulceration without co-prescription of an ulcer-healing drug (denominator)
- Patients aged ≥ 18 years prescribed warfarin or NOAC in combination with an oral NSAID (excluding aspirin) (numerator) / Patients aged ≥ 18 years prescribed warfarin or NOAC (denominator)
- Patients aged ≥ 18 years prescribed warfarin or NOAC and an anti-platelet drug in combination without co-prescription of an ulcer-healing drug (numerator) / Patients aged ≥18 years prescribed warfarin or NOAC without co-prescription of an ulcer-healing drug (denominator)
- Patients aged ≥18 years prescribed aspirin in combination with another anti-platelet drug without co-prescription of an ulcer-healing drug (numerator)/Patients aged ≥ 18 years prescribed aspirin without co-prescription of an ulcer-healing drug (denominator)
- Patients aged ≥ 18 years with asthma prescribed a long-acting beta-2 agonist inhaler not also prescribed an inhaled corticosteroid (numerator) / Patients aged ≥18 years with asthma prescribed a long-acting beta-2 agonist inhaler (denominator)
- Patients aged ≥ 18 years who have a diagnosis of heart failure prescribed an oral NSAID (excluding aspirin) (numerator)/ Patients aged ≥ 18 years who have a diagnosis of heart failure (denominator)
- Patients aged ≥ 65 years with a Read code for dementia but no Read code for psychosis prescribed antipsychotic drugs for >6 weeks (numerator)/ Patients aged ≥ 65 years with a Read code for dementia but no Read code for psychosis (denominator)

- Patients aged ≥18 years with an eGFR <45 prescribed an oral NSAID (excluding aspirin) (numerator) / Patients aged ≥18 years with an eGFR <45 (denominator).

Descriptive statistics:

To illustrate patients' demographic characteristics and diagnosis, descriptive statistics in terms of frequency counts and proportions were used.

For each record, the medication list during the study period was checked against the SFDA list of human medications and each medication was subsequently classified as either a prescription or OTC medication. If the patient's record showed that the patient had used OTC medication at any point during the 15 months, this was recorded in the data collection sheet as 'yes'. If the patient's record showed that the patient was using ≥ five concurrent medications at any point during the 15 months, this was also recorded in the data collection sheet as 'yes'.

Risk factors:

A regression technique allows the identification and description of the relationships that exist between variables. Regression is" *the relation of mean values of a dependent or regressand variable to independent or regressor variables (covariates)*".(106)

Several types of regression techniques exist. Two of the most widely used in research are: a) linear regression, which analyses continuous outcomes (dependent variable), and b) logistic regression, which analyses categorical outcomes (dependent variable).(119)

As a result, logistic regression was used to evaluate the strength and direction of the association between risk factors and outcome because I had categorical dependent variables (i.e. patients at risk outcome (*Y*): yes or no coded as 1 or 0) and independent variables (*x*) with 2 or more categories.(120)

Logistic regression is "*(Syn: logistic regression model) a statistical model for the probability that a binary variable Y equals 1 as a function of a covariate x, typically used when Y is an individual's disease indicator and x is the value of a risk factor or risk indicator*". (106)

Basic assumptions that must be met for logistic regression include independence of errors, the absence of multi-collinearity, and lack of strongly influential outliers. Additionally, there should be an adequate number of events per independent variable to avoid an overfit model,

with commonly recommended minimum ranging from 10 to 20 events per independent variable.(119)

The result of the regression analysis was presented in terms of OR; 95% confidence interval **(**CI). Significance measures of P <0.05 and 95% CI were used. CI is "*a range constructed around the sample statistic in such a way that the population parameter is included with a specified probability*".(121)

Each logistic regression involved the entry of a single dependent variable and a single independent variable. For the logistic regression modelling, the dependent variable was defined as the presence/absence of the outcome i.e. the presence/absence of patients at risk of medication error. The independent variables were age in years, gender, nationality, taking five or more drugs (polypharmacy) and using OTC medications.

For the interpretation of ORs with their 95% CIs, OR greater than 1 corresponds to 'positive effects' because they increase the odds. Those between 0 and 1 correspond to 'negative effects' because they decrease the odds. ORs of exactly 1 corresponds to 'no association'.(119)

A CI containing 1.0 for an OR means that we are less than 95% sure that a significant difference exists; a significance test of the difference would thus give P > 0.05. A confidence interval not including 1.0 for an OR means that we are more than 95% sure that a significant difference exists; a significance test of the difference would thus give P < 0.05. An interval bounded at one end by exactly 1.0 will give P= 0.05.(121)

Agreement between two data extractors:

For the categorical variable, Kappa coefficient is commonly used to determine the coefficient of agreement between the two independent data extractors.

A Kappa score: is "*a measure of the degree of nonrandom agreement between observers or measurements of the same categorical variable. Kappa coefficients are measures of correlation between categorical variables often used as reliability or validity coefficients".*(106)

The number of positive (error or risk) in the pilot study dataset is 196 in 200 patients. To be able to calculate the Kappa coefficient, the data were entered as a two-way table. For details on the Kappa coefficient method for calculation see Appendix 8.

For the interpretation of the Kappa coefficient, Landis and Koch suggested a Kappa value of less than 0.40 is considered poor-to-fair agreement, 0.41-0.60 is moderate agreement, 0.61-0.80 is felt to be substantial agreement, and 0.81-1.00 is considered almost perfect agreement.(122) Discrepancies were resolved by discussion between the two data extractors and by double-checking the records.

Using a retrospective cohort, missing data are common. I reported the number of, and reasons for, missing values, where possible. Removing subjects with missing data may produce biased results, unless the subjects with missing data are few. If there is a large proportion of missing data, a suitable multiple imputation technique can be used to reduce bias.

6.2.9 Ethics and regulatory approvals

I was aware of the ethical considerations in my study and the responsibility of dealing with data. The WHO's report 'Ethical issues in patient safety research' states in the privacy and confidentiality guideline that "*every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information*".(123) Confidentiality and privacy of the data were maintained throughout this study. To ensure anonymity of participants, all participants' personal data or identifiers were treated confidentially by giving each participant a code number, thus anonymising the data in any future publications.

An inventory of medical record numbers mapping identifiers to patient's code number was also stored as a hard copy in a secure location in the clinic (i.e. locked office).

Regarding EHR searching, patients were not contacted, and I did not record any patient identifier information such as names, addresses, and medical record numbers that could be used to link data to participants. According to the KFSH&RC guidelines and policy of the REC, the research method does not require a subject's consent. As stated in the 'Research that may be exempt from REC review' section:

> "*It is important to note that the study of existing data (retrospective chart reviews) or the use of discards of tissue taken for clinical reasons can ONLY be exempted from REC review IF the information is recorded in such a manner that the subjects cannot be identified, either directly or through a code linked to the subject (i.e., the identity of the subject is NOT or may NOT be readily ascertained by the investigator or associated with the information). It is also important to note that the types of research that can be exempted must pose NO risks to the subjects*".(109)

The data collected from the EHRs were used for the research purpose only. Research protocols that may be eligible for exemption from REC review must be submitted to the Office of Research Affairs for registration and approval by the research advisory council (i.e., the Clinical Research Committee or Basic Research Committee). Each protocol must also contain a statement that justifies the request for exemption.(109)

I simultaneously received ethical approval for Phases 2 and 3 of my research programme from the Clinical Research Committee and the REC of the institution's Office of Research Affairs, KFSH&RC, Riyadh, SA (see Section 5.2.6). (Appendix 9)

6.2.10 Reporting

The methodology of the Phase 3 pilot retrospective cohort study was reported using the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist (124) and the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement.(125) (see Appendix 11).

6.3 Results

At sampling, the number of all patients who visited the Family Medicine department two weeks before data collection was 1,253. I and SK collected the required information from 200 electronic records after excluding patients who were aged under 18 years, registered for less than 15 months, not on medications, or who had died, left the clinic or did not attend (see Box 5-1). The pilot retrospective study was conducted over a 15-month period between 01 February 2016 and 31 May 2017.

The percentages of adults in the age range 18-64 and 65 years or over were 83.0% and 17.0%, respectively. The majority of the study population was of Saudi nationality (74.0%). Table 6-1 summarises the data relating to the adults' characteristics.

The agreement between the two independent data extractors was substantial (Kappa 0.69). All discrepancies were resolved by discussion and by double-checking the records. For details on the Kappa coefficient result see Appendix 8.

In the pilot study stage, no missing data were found.

Variable			**Mean (years; 95% CI)**	
Age			(50.1; 95% CI 47.9 to 52.4)	
Variable			**Count (%)**	
Age	18-64 years		166 (83.0%)	
	≥ 65 years		34 (17.0%)	
Gender	Male		72 (36.0%)	
	Female		128 (64.0%)	
Nationality	Saudi		148 (74.0%)	
	Non-Saudi		52 (26.0%)	
Polypharmacy	Yes: ≥ 5 medications		119 (59.5%)	
	No: 1-4 medications		81 (40.5%)	
OTC medicines	Yes: using OTC		186 (93.0%)	
	No: not using OTC		14 (7.0%)	
Diagnosis	**Cardiac and vascular disorder**		**Gastrointestinal disorder**	
	Cardiac arrhythmias	2 (1.0%)	Ulcer	1 (0.5%)
	Dyslipidaemia	79 (40%)	Gastritis	9 (4.5%)
	Essential hypertension	85 (42.5%)	History of H. pylori	6 (3.0%)
	Heart failure	5 (2.5%)	**Renal disorder**	
	Ischemic heart disease	9 (4.5%)	Chronic kidney disease	8 (4.0%)
	Pulmonary disorder		**Arthritic disorder**	
	Asthma	27 (13.5%)	Osteoarthritis	27 (13.5%)
	COPD	1 (0.5%)	Osteoporosis	2 (1.0%)
	Rhinitis	20 (10.0%)	**Endocrine disorder**	
	Psychiatric disorder		Hypo/hyperthyroidism	34 (17.0%)

	Depression	13 (6.5%)	Diabetes mellitus	73 (36.5%)
	Bipolar	1 (0.5%)		
	Dementia	3 (1.5%)		

Table 6-1. Pilot study demographic characteristics.

6.3.1 Proportions of errors in patients at risk of each outcome measure

We reviewed the electronic record of each patient and extracted the relevant data retrospectively within the study period.

For each record and for each of the outcomes of interest, we identified whether a particular patient was at risk and whether a relevant prescribing or monitoring error had been made. The details are shown in Table 6-2.

Outcome measures	**Numerators**	**Denominators**	**Proportion of errors in patients at risk (%); 95% CI**
Primary outcomes			
1. Patients with a history of peptic ulcer who had been prescribed a non-selective NSAID without co-prescription of a PPI	0	1	0
(2a) Patients with asthma who had been prescribed a β-blocker	3	4	75.0; 95% CI -4.6 to 154.6
3. Patients aged 75 years and older who had been prescribed an ACE inhibitor or a loop diuretic long-term who had not had a computer-recorded check of their renal function and electrolytes in the previous 15 months	0	1	0
Secondary outcomes			
(2b) Patients with asthma [and no	4	24	16.7; 95% CI

Outcome measures	Numerators	Denominators	Proportion of errors in patients at risk (%); 95% CI
history of CHD] who had been prescribed a β-blocker			0.6 to 32.7
4. Proportions of women with a past medical history of venous or arterial thrombosis who had been prescribed the combined oral contraceptive pill	0	1	0
5. Patients receiving methotrexate for at least 3 months who had not had a full blood count recorded (5a), or liver function test (5b), in the previous 3 months	0	0	Not calculable
6. Patients receiving warfarin for at least 3 months who had not had a recorded check of their INR in the previous 12 weeks	0	2	0.0
7. Patients receiving lithium for at least 3 months who had not had a recorded check of their lithium concentrations in the previous 3 months	1	1	100.0
8. Patients receiving amiodarone for at least 6 months who had not had a thyroid function test in the previous 6 months	0	0	Not calculable
9. Patients receiving prescriptions of methotrexate without instructions that the drug should be taken every week	0	0	Not calculable
10. Patients receiving prescriptions of	0	0	Not calculable

Outcome measures	Numerators	Denominators	Proportion of errors in patients at risk (%); 95% CI
amiodarone for at least 1 month who are receiving a dose of more than 200 mg per day			
Composite secondary outcome measures			
11. Patients with at least one prescription problem (a combination of outcome measures 1, 2, and 4)	7	30	23.3; 95% CI 7.3 to 39.4
12. Patients with at least one monitoring problem (a combination of outcome measures 3, 5, 6, 7, and 8)	1	4	25.0; 95% CI -54.6 to 104.6
Additional revised updated outcomes measures			
13. Prescription of an oral NSAID, without co-prescription of an ulcer-healing drug, to a patient aged ≥ 65 years	6	27	22.2; 95% CI 5.5 to 38.9
14. Prescription of an anti-platelet drug without co-prescription of an ulcer-healing drug, to a patient with a history of peptic ulceration	0	1	0.0
15. Prescription of warfarin or NOAC in combination with an oral NSAID	0	5	0.0
16. Prescription of warfarin or NOAC and an anti-platelet drug in combination without co-prescription of an ulcer-healing drug	3	4	75.0; 95% CI -4.6 to 154.6
17. Prescription of aspirin in combination with another anti-platelet	4	46	8.7; 95% CI 0.2 to 17.2

Outcome measures	Numerators	Denominators	Proportion of errors in patients at risk (%); 95% CI
drug without co-prescription of an ulcer-healing drug			
18. Prescription of a long-acting beta-2 agonist inhaler (excluding combination products with inhaled corticosteroid) to a patient with asthma who is not also prescribed an inhaled corticosteroid	0	0	Not calculable
19. Prescription of an oral NSAID to a patient with heart failure	2	5	40.0; 95% CI -28.0 to 108.0
20. Prescription of antipsychotics for > 6 weeks in a patient aged ≥ 65 years with dementia but not psychosis	1	3	33.3; 95% CI -110.1 to 176.8
21. Prescription of an oral NSAID to a patient with eGFR < 45	0	5	0
Period prevalence	32 total number of errors	200 total patients	16.0; 95% CI 8.2 to 23.8
Period prevalence	Total of 20 patients with at least one error	200 total patients	10.0; 95% CI 5.8 to 14.2

Table 6-2. Pilot study proportion of errors in patients at risk of each primary, secondary, composite and revised updated outcome measure described using numerators, denominators and percentage, at patient level.

Outcome 1: Proportion of patients prescribed a NSAID (excluding aspirin), without a PPI among patients with a history of peptic ulcer

Only one patient had a history of peptic ulcer without PPI. This patient was not on any NSAID.

Outcome 2a: Proportion of β-blocker users among patients with asthma

Four patients had a history of asthma. Out of the patients at risk, 75.0% of the patients had at least one prescription of β-blocker oral preparations or eye drops. The prescribed β-blockers were carvedilol and metoprolol.

Outcome 2b: Proportion of β-blocker users among patients with asthma and without CHD

Twenty-four patients had a history of asthma and no history of CHD. Out of the patients at risk, 16.7% had received at least one prescription of β-blocker oral preparations or eye-drops. The prescribed β-blockers were atenolol, metoprolol and timolol eye drops.

Outcome 3: Proportion of patients without check of renal function among patients aged ≥ 75 years on ACEI or loop diuretics

There was one patient aged ≥ 75 years with evidence of long-term (> 15 months) prescription of ACE inhibitors or loop diuretics. This patient had received a check of his renal function in the previous 15 months.

Outcome 4: Proportion of oral contraceptive users among female patients with venous or arterial thromboembolism

One female patient had venous or arterial thromboembolism. The patient was not on any oral contraceptive.

Outcome 5a, 5b: Proportion of patients without full blood count or liver function test among methotrexate users

There were no patients with evidence of at least three months of prescribing of methotrexate.

Outcome 6: Proportion of patients without INR among warfarin users

There were two patients with evidence of at least three months of prescribing of warfarin. None of the patients at risk had no INR recording in the previous three months.

Outcome 7: Proportion of patients without a lithium level check among lithium users

There was one patient with evidence of at least three months of prescribing of lithium. This patient at risk had not had a lithium level check in the previous three months.

Outcome 8: Proportion of patients without thyroid function test among amiodarone users

None of the patients were using amiodarone.

Outcome 9: Proportion of patients without instructions taken every week among methotrexate users

None of the patients were using methotrexate.

Outcome 10: Proportions of patients receiving a dose of more than 200 mg per day among amiodarone users

None of the patients were using amiodarone.

Outcome 11: Proportion of patients with at least one prescribing problem (i.e. Outcomes 1, 2 and 4) among patients at risk of at least one prescribing problem

There were 30 "at risk" patients with at least one prescribing problem. Of the patients at risk, 23.3% had experienced at least one prescribing problem.

Outcome 12: Proportion of patients with at least one monitoring problem (i.e. Outcomes 3, 5 (a or b), 6, 7 and 8) among patients at risk of one monitoring problem

There were four "at risk" patients with at least one monitoring problem. Of the patients at risk, 25.0% had at least one monitoring problem.

Outcome 13: Proportion of patients prescribed an oral NSAID (excluding aspirin), without co-prescription of an ulcer-healing drug among patients aged ≥ 65 years

Twenty-seven patients were aged ≥ 65 years without co-prescription of an ulcer-healing drug. Of the patients at risk, 22.2% had been given at least one prescription of an oral NSAID (except aspirin) without co-prescription of an ulcer-healing drug. The NSAIDs prescribed were diclofenac, celexoxib, meloxicam and naproxen.

Outcome 14: Proportion of patients prescribed an anti-platelet drug without co-prescription of an ulcer-healing drug among peptic ulcer patients

Only one patient had a history of peptic ulcer without co-prescription of an ulcer-healing drug. The patient was not on any anti-platelet drug.

Outcome 15: Proportion of patients prescribed an oral NSAID (excluding aspirin)among warfarin or NOAC users

Five patients had been prescribed warfarin or NOAC. None of the patients had at least one prescription of an oral NSAID.

Outcome 16: Proportion of patients prescribed an anti-platelet drug without co-prescription of an ulcer-healing drug among warfarin or NOAC users

Four patients had been prescribed warfarin or NOAC without co-prescription of an ulcer-healing drug. Out of the patients at risk, 75.0% had been given at least one prescription of an anti-platelet drug. The anti-platelet drugs prescribed were aspirin and clopidogrel.

Outcome 17: Proportion of patients prescribed an anti-platelet drug without co-prescription of an ulcer-healing drug among aspirin users

Forty-six patients had been prescribed aspirin without co-prescription of an ulcer-healing drug. Out of the patients at risk, 8.7% had been given at least one prescription of an anti-platelet drug. The anti-platelet drug prescribed was clopidogrel.

Outcome 18: Proportion of patients prescribed a long-acting beta-2 agonist inhaler (excluding combination products with inhaled corticosteroid) who are not also prescribed an inhaled corticosteroid among asthma patients

All patients with asthma had been prescribed a long-acting beta-2 agonist inhaler (combination products with inhaled corticosteroids).

Outcome 19: Proportion of patients prescribed an oral NSAID (excluding aspirin) among patients with heart failure

Five patients had heart failure. Out of the patients at risk, 40.0% had been given at least one prescription of an oral NSAID. The NSAID prescribed was meloxicam.

Outcome 20: Proportion of patients prescribed an antipsychotic for > 6 weeks among patients aged ≥ 65 years with dementia but not psychosis

Three patients aged ≥ 65 years had dementia (not psychosis). Out of the patients at risk, 33.3% had been given at least one prescription of an antipsychotic for > 6 weeks. The antipsychotic prescribed was quetiapine.

Outcome 21: Proportion of patients prescribed an oral NSAID (excluding aspirin) among patients with eGFR < 45

There were five patients with eGFR <45. Out of the patients at risk, none had been given at least one prescription of an oral NSAID.

6.3.2 Overall period prevalence rate

We found a total of 32 prescribing/monitoring errors during the study period, categorised as the following: 23 prescribing errors (contraindications), one monitoring error and 8 Composite secondary outcome measures prescribing/monitoring errors.

Overall period prevalence

Numerator = the number of patients experiencing one or more medication error at any time during the 15 month period = 20 patients.
Denominator = the total number of patients in the study population = 200 patients.
The overall period prevalence of patients with at least one medication error over 15 months = 20 (numerator) / 200 (denominator) = 10.0% (95% CI 5.8 to 14.2).

Numerator = the number of medication errors at any time during the 15 month period = 32 patients.
Denominator = the total number of patients in the study population = 200 patients.
The overall period prevalence of medication errors over 15 months= 16.0% (95% CI 8.2 to 23.8).

6.3.3 Risk factors

Risk factors that significantly predicted the overall patients at risk of medication errors were patient's age of ≥65 years and using OTC medications.

On the basis of the estimated ORs, patients aged ≥ 65 years were estimated to be 35 times more likely to be at risk of experiencing medication error than those aged 18-64 years (OR 35.1; 95% CI 8.1 to 151.9). Patients using OTC medications were estimated to be four times more likely to be at risk of experiencing medication error than those patients not using OTC (OR 3.8; 95% CI 1.1 to 12.5). There was no association between most of the risk factors and patients at risk outcomes number 1, 3, 4, 5a and 5b, 7, 8, 9, 10, 14, and 18. (See Table 6-3)

	Age (≥ 65 / 18-64 years) **OR**; 95% CI	P value	**Gender** (male /female) **OR**; 95% CI	P value	**Nationality** (Saudi / non-Saudi) **OR**; 95% CI	P value	Taking five or more drugs (**Polypharmacy)** (yes/no) **OR**; 95% CI	P value	**OTC** (yes/no) **OR**; 95% CI	P value
Overall patients at risk of experiencing medications errors										
	35.1; 8.1 to 151.9	0.00	0.5; 0.3 to 0.9	0.02	0.2; 0.1 to 0.5	0.00	0.2; 0.1 to 0.35	0.00	3.8; 1.1 to 12.5	0.03
Number of individual patients at risk outcomes										
2a	1.6; 0.2 to 16.3	0.67	0.2; 0.0 to 1.8	0.14	NA	-	NA	-	NA	-
2b	1.3; 0.5 to 3.9	0.59	0.6; 0.3 to 1.5	0.29	0.4; 0.1 to 1.3	0.12	0.3; 0.1 to 0.9	0.04	1.2; 0.3 to 5.9	0.79
6	5.0; 0.3 to 81.9	0.26	NA	-	NA	-	1.5; 0.1 to 23.9	0.79	NA	-
11	1.6; 0.6 to 4.1	0.32	0.5; 0.2 to 1.1	0.09	0.3; 0.1 to 0.9	0.04	0.3; 0.1 to 0.8	0.02	0.9; 0.2 to 4.4	0.94
12	5.1; 0.7 to	0.11	1.7; 0.2 to	0.65	NA	-	0.5; 0.0 to 4.7	0.53	NA	-

	Age (≥ 65 / 18-64 years) **OR**; 95% CI	P value	**Gender** (male /female) **OR**; 95% CI	P value	**Nationality** (Saudi / non-Saudi) **OR**; 95% CI	P value	Taking five or more drugs (**Polypharmacy)** (yes/no) **OR**; 95% CI	P value	**OTC** (yes/no) **OR**; 95% CI	P value
	37.7		16.7							
13	NA	-	0.8; 0.3 to 1.8	0.58	NA	-	0.3; 0.1 to 0.8	0.02	2.8; 0.8 to 9.8	0.09
15	1.2; 0.1 to 11.3	0.86	0.4; 0.05 to 2.2	0.28	0.7; 0.1 to 6.5	0.76	0.35; 0.0 to 3.2	0.36	NA	-
16	1.6; 0.2 to 16.3	0.67	0.6; 0.1 to 4.0	0.56	NA	-	0.5; 0.0 to 4.7	0.53	NA	-
17	4.7; 2.15 to 10.3	0.00	0.6; 0.3 to 1.15	0.12	0.35; 0.1 to 0.9	0.03	0.15; 0.1 to 0.4	0.00	5.2; 1.7 to 15.9	0.00
19	22.0; 2.4 to 203.7	0.01	0.1; 0.0 to 1.2	0.07	NA	-	NA	-	NA	-
20	NA	-	0.3; 0.0 to 3.1	0.29	NA	-	0.7; 0.1 to 8.2	0.80	NA	-
21	22.0; 2.4 to	0.01	0.4; 0.05 to	0.28	NA	-	NA	-	NA	-

	Age (≥ 65 / 18-64 years) **OR**; 95% CI	P value	**Gender** (male /female) **OR**; 95% CI	P value	**Nationality** (Saudi / non-Saudi) **OR**; 95% CI	P value	Taking five or more drugs (**Polypharmacy)** (yes/no) **OR**; 95% CI	P value	**OTC** (yes/no) **OR**; 95% CI	P value
	203.7		2.2							

Table 6-3. Pilot study association between risk factors and patients at risk of medication error outcome. (Data obtained from logistic regression models). NA: No association. OR = 1.

6.4 Chapter summary

In this pilot retrospective study, a random sample was selected from the Family Medicine and Polyclinics in KFSH&RC, Riyadh, SA. EHRs were screened and relevant data collected to investigate the period prevalence and risk factors of patient at risk of clinically important errors in the medicine management in adults. The outcome measures used included the prescription of aspirin, anti-platelet, antipsychotics, β-blockers, NSAIDs, NOACs and warfarin and the monitoring of ACE inhibitor or loop diuretics, amiodarone, methotrexate, lithium, and warfarin.

The overall period prevalence of patients with at least one medication error over 15 months was (10.0%; 95% CI 5.8 to 14.2). The overall period prevalence of medication errors over 15 months was (16.0%; 95% CI 8.2 to 23.8). The pilot study suggested that clinically important errors in medicine management in adults are common. The highest risk of prescribing error was in patients with asthma who had been prescribed a β-blocker and in patient prescribed warfarin or NOAC and an anti-platelet drug in combination without co-prescription of an ulcer-healing drug. A monitoring error was found in one patient receiving lithium for at least three months who had not received a recorded check of their lithium concentrations in the previous three months. Risk factors that significantly predicted the overall patients at risk of medication errors were patient's age of ≥65 years and using OTC medications. However, the data suggested that other factors might be identified in the larger planned follow-on study (see Chapter 7).

The findings from this phase of the research suggested that the continuation of the cohort study was important. This study's approval and protocol were then used for the main cohort study. The continuation of Phase 4 was undertaken without excluding any of the outcome measures, because any outcomes not appearing in this phase may appear when screening a higher number of records. Clearly, more long-term data were needed to explore further the effects of physician-related risk factors on the patients at risk of experiencing medication errors. This goal was accomplished with a larger-scale cohort study that is discussed in the next chapter.

Chapter Seven: Phase 4: Retrospective Cohort Study Investigating the Epidemiology of Medication Errors in Adults Using Electronic Health Records in Riyadh, Saudi Arabia

7.1 Introduction

The epidemiology of medication errors among patients in ambulatory care has never been studied in SA as shown in my systematic review (Chapter 4).(113) Therefore, in 2017, as part of this research, a feasibility and pilot study (Phases 2 and 3) were initiated to test the feasibility and reliability of using data extraction from the EHRs of KFSH&RC Family Medicine and Polyclinics, Riyadh, SA (see Chapters 5 and 6). The purpose of Phase 3 was to pilot plans to determine the period prevalence of clinically important errors in medicine management, as well as their risk factors, and to inform sample size calculations for a retrospective cohort study (Phase 4). No changes to the methodology of the pilot retrospective cohort study were made, except for adding physician-related risk factors (see Section 7.2.3). Phase 4 of my research focused only on the medication errors as in Phases 2 and 3.

This chapter reports on an investigation into the epidemiology of clinically important errors in medicine management as defined by the PINCER trial.(85) The results from this study will assist in allocating resources and improving the quality of healthcare provided in ambulatory and primary care in SA.

It should be noted that Phase 1 of this research focused on both medication errors and error-related ADEs, but Phases 2, 3 and 4 focused solely on medication errors.

7.2 Methods

7.2.1 Study design

A cohort study is *"The analytic epidemiological study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed—or exposed in different degrees—to a factor or factors hypothesized to influence the occurrence of a given outcome".*(106)

The choice of study design in research depends on many factors, including prior research,

availability of study participants, funding, and time constraints.(126) An observational study design, rather than an intervention design, was chosen for my research considering the limited research team and time available. There are three main types of observational studies: a) cross-sectional, b) case-control and c) cohort study. All three study designs have the advantage of the ability to control for multiple confounders, where a confounder is "*a variable that can be used to decrease confounding bias (bias of the estimated effect of an exposure on an outcome due to the presence of common causes of the exposure and the outcome) when properly adjusted for*".(106) The case-control study was excluded because it cannot measure the prevalence of outcome and can only assess one outcome. In addition, the cross-sectional design was excluded because it only provides a snapshot of a particular sample at a given point in time, unlike longitudinal studies that look at a sample over an extended period.(126)

A cohort design was chosen for this study because: a) of its ability to assess multiple exposures, b) it can assess multiple outcomes, and c) of its ability to either follow-up over a period of time to identify which participants develop the outcome(s) of interest (prospective), or look back at data that were created in the past, prior to the development of the outcome (retrospective).(126)

A retrospective cohort study design was undertaken to measure the period prevalence of the primary, secondary, composite secondary and revised updated outcome measures and risk factors.(85, 107)

7.2.2 Participants and sampling

A random sample of patients visiting the Family Medicine and Polyclinics was selected.

Subjects were selected from the Family Medicine and Polyclinics at KFSH&RC. Sampling took one month in 2017; follow-up was carried out retrospectively, over the 15 months prior to the data extraction from 1 August 2016 to 30 November 2017. Data collection took three months (01 October 2017 to 31 December 2017) complying with the time limit set by the Saudi Bureau for fieldwork inside SA.(127) The retrospective cohort study flowchart (Figure 7-1) shows a description of the population and sample included.

For patients' inclusion and exclusion criteria see Chapter 6, Section 6.2.2.

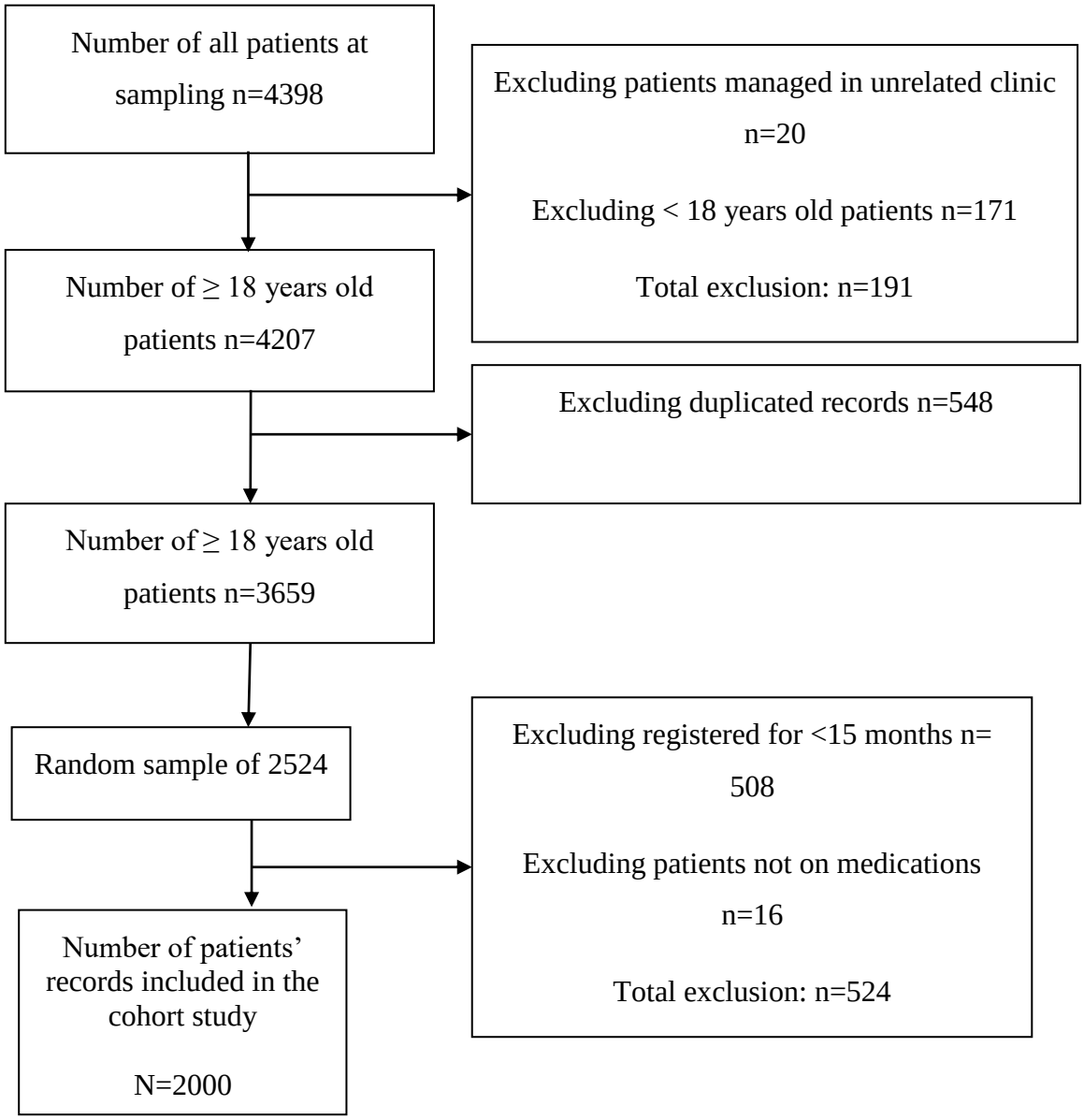

Figure 7-1. Cohort study flowchart outlines population and sample enrolment.

Method of sampling:

A list of all patients who visited the family medicine department one month before data collection (01 October 2017) was generated. One month was specified because the maximum duration that could be specified by the ICIS for generating a patient list was two weeks, which yielded around 1,500 records. Therefore, the patient list was generated twice to achieve the required sample size. A serial number was assigned to each record, after which paediatric patients were excluded. Then, numbers were selected at random from a table of random

numbers, until the desired sample size was attained.(106) Electronic records were randomly selected using a random number table generated using the 'simple random sample without replacement' function in STATA (version 14). Unfortunately, Saudi national data are not available to enable comparison between the baseline characteristics of the sample population and the whole population.

7.2.3 Variables

Baseline characteristics:

Patients' characteristic:

Patients' baseline characteristic variables recorded were age, gender, nationality (Saudi, non-Saudi), diagnosis or underlying conditions, OTC recorded at any point during the 15 months and polypharmacy (taking five or more medications at any point during the 15 months).

Physicians' characteristic:

Family medicine/general practice physicians' baseline characteristic variables recorded were age (18-50 years, ≥51 years), gender, nationality (Saudi, non-Saudi), number of physicians involved in each patient's care (one, more than one), certification (American, British, Canadian, Jordanian, or none) and number of years of experience (1-9 years, ≥ 10 years). A list of all physicians in the Family Medicine and Polyclinics was obtained and each physician assigned a code (e.g. PHa, PHb, etc.).

Exposures:

1. Prescribed medications and/or OTC drugs.
2. Patient and physician-related risk factors.

Outcome variables:

1. Period prevalence of the primary, secondary, composite secondary and revised updated outcome measures.

   For details of the primary, secondary, composite secondary and revised updated outcome measures see Chapter 5 (Box 5-1).(85, 107)

7.2.4 Data sources/measurement

Identification of outcomes

After selecting a random sample from the Family Medicine and Polyclinics, in-depth EHR screening involving assessment of diagnostic, medication list and laboratory data was undertaken in order to investigate the period prevalence of clinically important errors and patient and physician-related risk factors that were associated with patients at risk of clinically important errors in medicines management. The presence, or absence, of the primary, secondary, composite secondary and revised updated outcome measures (the numerator) and the denominator for each outcome measure was recorded. During this review of EHRs, I only focused on the outcomes detailed in Chapter 5 (Box 5-1).(85, 107)

The secondary trained data extractor Sarah Al-hathlool (SH) did a manual and independent data extraction on 10% (200 records) of the cohort study sample size (2000 records).(114, 128) Any discrepancies or disagreements were discussed and resolved by double-checking the records or via arbitration by the third reviewer (AK) if a decision could not be reached. In case of high discrepancies (poor-to-fair agreement), more records would be checked.

Data collection tool:

Data were extracted manually from the EHR using a paper-based data collection form. The reason for using the manual data extraction was explained in Section 5.5.5. An extensive summary description of all relative information available in the EHRs for the patient's demographics and outcome measures was collected (see Appendix 12). The paper data collection forms were stored in secure locations; locked office in the outpatient department in Riyadh, SA and the PhD office in Edinburgh, UK.

The information in the paper-based data collection tool was transferred to an electronic data sheet using an Excel spreadsheet to facilitate analysis. The electronic data sheet was stored in a password-protected computer and no patient identifying information was recorded.

7.2.5 Bias

See Chapter 6 Section 6.2.5 for a discussion on potential sources of bias and how I attempted to minimise the effects of these sources.

7.2.6 Study size

Every record needed a maximum of 15 minutes to scan and extract data. The largest sample size that was feasible was chosen, taking into account the time available, resources and research team; resulting in a total of 2000 records. See Chapter 6 section 6.2.6 for more details relating to this issue.

7.2.7 Data access and cleaning methods

See Chapter 6 Section 6.2.7 for a discussion on data access and cleaning methods. An inventory of medical record numbers, patients' code numbers and patients' attendance dates was used to ensure patients were not included in the dataset more than once.

7.2.8 Statistical methods

Microsoft Excel was used to process data and STATA (version 14) was used to analyse the data. See Chapter 6. Section 6.2.8 for further information relating to this matter.

Descriptive analysis:

To illustrate patients' demographic characteristics and diagnosis, descriptive statistics in terms of frequency counts and proportions were used.

Risk factors:

To evaluate the association of risk factors and outcome, I used a logistic regression model. The results of the regression analysis were presented in terms of (OR; 95% CI). Each logistic regression involved the entry of a single dependent variable and a single independent variable.

The patient and physician-related independent variables were detailed in Section 7.2.3. The dependent variable was defined as the presence/absence of the outcome i.e. the presence/absence of patients at risk of medication error. Significance measures $P < 0.05$ and 95% CI are used.

Agreement between two data extractors:

Cohen's Kappa coefficient was also calculated see Chapter 6, Section 6.2.8 for details on Kappa score agreements. If poor-to-fair agreement was achieved, more samples would be checked for their reliability.

The number of observations with positive (error or risk) in the cohort study dataset is 48 in 200 Patients. The data were entered as a two-way table. For details on the Kappa coefficient method for calculation see Appendix 8.

Comparison:

It should be emphasised that the results of the UK-based PINCER trial cannot be directly compared to the cohort study, because the PINCER trial is an interventional study. However, it was possible to compare the study's results with the QRESEARCH analysis of secular trends i.e. the large national QRESEARCH general practice database, one of the largest aggregate general practice electronic databases worldwide, consisting of 1,500 general practices.(129, 130)

7.2.9 Ethics and regulatory approvals

Since no major changes were applied after the pilot phase, the ethical approval for the pilot retrospective cohort study remained valid. I had received ethical approval for Phases 2 and 3 from the Clinical Research Committee and the REC of the institution's Office of Research Affairs, KFSH&RC, Riyadh, SA (see Section 5.2.6) (see Appendix 9). In addition, the proposal for data collection and extraction from 2000 electronic records, together with the addition of physician-related risk factors into the cohort study, was reviewed by the REC and approved (Appendix 13).

7.2.10 Reporting

The methodology for Phase 4, retrospective cohort study, follows the STROBE checklist (124) and RECORD statement (see Appendix 14).(125)

7.3 Results

At sampling, the number of all patients who visited the Family Medicine department one month before data collection was 4,398. I collected the required information of 2000 electronic records after excluding patients aged <18 years, patients registered for <15 months, those who were not on medications, and those who had died, left the clinic or had not attended. (See Figure 7-1**Figure 7-1**).

The percentages of adults in the age range 18-64 and ≥65 years were 83.85% and 16.15%, respectively. The majority of the study's population was of Saudi nationality (67.2%); Table 7-1 summarises the data on adults' characteristics.

The agreement between the two independent data extractors for 200 records was substantial (Kappa 0.8). All discrepancies were resolved by discussion and by double-checking the records. For details on the Kappa coefficient result see Appendix 8.

Variable			**Mean (years; 95% CI)**	
Age			(49.9; 95% CI 48.2 to 49.6)	
Variable			**Count (%)**	
Age	18-64 years		1,677 (83.85%)	
	≥ 65 years		323 (16.15%)	
Gender	Male		698 (34.9%)	
	Female		1,302 (65.1%)	
Nationality	Saudi		1,344 (67.2%)	
	Non-Saudi		656 (32.8%)	
Polypharmacy	Yes: ≥ 5 medications		1,115 (55.75%)	
	No: 1-4 medications		885 (44.25%)	
OTC medicines	Yes: using OTC		1,899 (94.95%)	
	No: not using OTC		101(5.05%)	
Diagnosis	**Cardiac and vascular disorder**		**Gastrointestinal disorder**	
	Cardiac arrhythmias	18 (0.9%)	Ulcer	5 (0.25%)

	Dyslipidaemia	819 (40.95%)	Gastritis	90 (4.5%)
	Essential hypertension	816 (40.8%)	History of H. pylori	22 (1.1%)
	Heart failure	14 (0.7%)	**Renal disorder**	
	Ischemic heart disease	69 (3.45%)	Chronic kidney disease	60 (3.0%)
	Pulmonary disorder		**Arthritic disorder**	
	Asthma	250 (12.5%)	Osteoarthritis	180 (9.0%)
	COPD	5 (0.25%)	Osteoporosis	44 (2.2%)
	Rhinitis	324 (16.2%)	**Endocrine disorder**	
	Psychiatric disorder		Hypo/hyperthyroidism	353 (17.65%)
	Depression	164 (8.2%)	Diabetes mellitus	595 (29.75%)
	Dementia	17 (0.85%)		

Table 7-1. Cohort study demographic characteristics.

7.3.1 Proportions of errors in patients at risk of each outcome measure

The results were compared with the QRESEARCH analysis of secular trends. The overall period prevalence of the first 12 clinically important errors in medicine management estimates was (3.4%; 95% CI 2.2 to 4.6) in this research compared with 0.9% for the QRESEARCH analysis of secular trends.(129) The distribution of each estimate for the outcome measures are set out below: in my study, higher period prevalence estimate were found in Outcomes 2a and 2b (asthma and β-blocker), Outcome 6 (warfarin and INR), Outcome 7 (lithium and lithium level), Outcome 11 (at least one prescription error) and Outcome 12 (at least one monitoring error).

I could not estimate rates for the following outcomes, because there were no events: Outcome 1 (peptic ulcer and NSAID without an ulcer-healing drug), Outcome 3 (ACE inhibitor / diuretics and lab test), Outcome 4 (venous or arterial thromboembolism and arterial thrombosis and combined oral contraceptives), Outcome 5a (methotrexate and full blood count, and 5b: methotrexate and liver function test). For Outcome 8 (amiodarone and thyroid function test) and Outcome 10 (amiodarone dose) there was no patient on amiodarone.

There follows a comparison of this study with the QRESEARCH analysis of secular trends results (see Table 7-2).

	Cohort study			QRESEARCH analysis of secular trends (129)			
Outcome measures	**Numerator**	**Denominator**	**Proportion of errors in patients at risk (%); 95% CI**	**Numerator**	**Denominator**	**Proportion of errors in patients at risk (%)**	**Median proportion of errors in patients at risk interquartile range (IQR)**
Primary outcomes							
1.Patients with a history of peptic ulcer who have been prescribed a non-selective NSAID without co-prescription of a PPI	0	4	0	1182	30204	4	3.45 (1.5 to 5.7)
(2a) Patients with asthma who have been prescribed a β-blocker	7	13	53.8; 95% CI 22.5 to 85.2	8130	324778	3	2.4 (1.75 to 3.1)
3.Patients aged 75 years and older who have been	0	11	0	8461	79496	11	9.2 (5.2 to 14.3)

	Cohort study			QRESEARCH analysis of secular trends (129)			
prescribed an ACE inhibitor or a loop diuretic long-term who have not had a computer-recorded check of their renal function and electrolytes in the previous 15 months							
Secondary outcomes							
(2b) Patients with asthma [and no history of CHD] who had been prescribed a β blocker	21	241	8.7; 95% CI 5.1 to12.3				1.55 (1.1 to 2.2)
4.Proportions of women with a past medical history of venous or arterial thrombosis who had been prescribed the combined oral contraceptive pill	0	4	0	223	27225	0.8	0 (0 to 0)
5.Patients receiving	(5a) 0	(5a) 14	(5a) 0	(5a)	(5a) 6424	(5a) 22	(5a) 16.7 (3.45 to

	Cohort study			QRESEARCH analysis of secular trends (129)			
methotrexate for at least 3 months who had not had a full blood count recorded (5a), or liver function test (5b), in the previous 3 months	(5b) 0	(5b) 14	(5b) 0	1435 (5b) 1495	(5b) 6424	(5b) 23	46.7) (5b) 20.0 (4.55 to 46.7)
6.Patients receiving warfarin for at least 3 months who had not had a recorded check of their INR in the previous 12 weeks	4	16	25.0; 95% CI 1.2 to 48.8	As median			4.0 (1.2 to 12.5)
7.Patients receiving lithium for at least 3 months who had not had a recorded check of their lithium concentrations in the previous 3 months	2	2	100.0; 95% CI 100.0 to 100.0	985	3245	30	28.6 (12.5 to 46.6)
8.Patients receiving	0	0	Not calculable	2114	4613	33	50.0 (30.0 to

	Cohort study			QRESEARCH analysis of secular trends (129)			
amiodarone for at least 6 months who had not had a thyroid function test in the previous 6 months							66.7)
9.Patients receiving prescriptions of methotrexate without instructions that the drug should be taken every week	0	14	0				
10.Patients receiving prescriptions of amiodarone for at least 1 month who are receiving a dose of more than 200 mg per day	0	0	Not calculable				
Composite secondary outcome measures							
11.Patients with at least one prescription problem	28	259	10.8; 95% CI 7.0 to 14.6				2.45 (1.8 to 3.1)

	Cohort study			QRESEARCH analysis of secular trends (129)			
(a combination of outcome measures 1, 2, or 4)							
12.Patients with at least one monitoring problem (a combination of outcome measures 3, 5, 6, 7, and 8)	6	43	13.95; 95% CI 3.2 to 24.7				12.4 (7.8 to 19.0)
Period prevalence	68 total number of errors	2000 total patients	3.4; 95% CI 2.2 to 4.6	24,025 total number of errors	2,779,781 total patients	0.9	
Period prevalence	Total of 33 patients with at least one error	2,000 total patients	1.65; 95% CI 1.1 to 2.2				
Additional revised updated outcomes measures							
13.Prescription of an oral NSAID, without co-	52	269	19.3; 95% CI 14.6 to 24.1				

	Cohort study			QRESEARCH analysis of secular trends (129)
prescription of an ulcer-healing drug, to a patient aged ≥65 years				
14.Prescription of an anti-platelet drug without co-prescription of an ulcer-healing drug, to a patient with a history of peptic ulceration	1	4	25.0; 95% CI - 54.6 to104.6	
15.Prescription of warfarin or NOAC in combination with an oral NSAID	2	32	6.25; 95% CI -2.6 to 15.1	
16.Prescription of warfarin or NOAC and an anti-platelet drug in combination without co-prescription of an ulcer-healing drug	11	22	50.0; 95% CI 27.3 to 72.7	
17.Prescription of aspirin	23	344	6.7; 95% CI 4.0 to	

	Cohort study			QRESEARCH analysis of secular trends (129)
in combination with another anti-platelet drug without co-prescription of an ulcer-healing drug			9.3	
18.Prescription of a long-acting beta-2 agonist inhaler (excluding combination products with inhaled corticosteroid) to a patient with asthma who is not also prescribed an inhaled corticosteroid	0	0	Not calculable	
19.Prescription of an oral NSAID to a patient with heart failure	3	14	21.4; 95% CI -3.15 to 46.0	
20.Prescription of antipsychotics for >6weeks in a patient aged ≥ 65 years with dementia but not	2	17	11.8; 95% CI -5.3 to 28.8	

	Cohort study			QRESEARCH analysis of secular trends (129)
psychosis				
21.Prescription of an oral NSAID to a patient with eGFR < 45	0	38	0	
Period prevalence	162 total number of errors	2000 total patients	8.1; 95% CI 6.5 to 9.7	
Period prevalence	Total of 117 patients with at least one error	2,000 total patients	5.85; 95% CI 4.8 to 6.9	

Table 7-2. Cohort study proportion of errors in patients at risk of each primary, secondary, composite and revised updated outcome measure described using numerators, denominators and percentage, at patient level comparing it with the QRESEARCH analysis of secular trends.

Outcome 1: Proportion of patients prescribed a NSAID (excluding aspirin), without a PPI among patients with a history of peptic ulcer

Four patients had a history of peptic ulcer without PPI. None of the patients had been prescribed NSAID.

Outcome 2a: Proportion of β-blocker users among patients with asthma

Thirteen patients had a history of asthma. Out of the patients at risk, 53.8% had at least one prescription of β-blocker oral preparations or eye drops. The prescribed β-blockers were atenolol, carvedilol and metoprolol.

Outcome 2b: Proportion of β-blocker users among patients with asthma and without CHD

Two hundred and forty-one patients had a history of asthma and no history of CHD. Out of the patients at risk, 8.7% had received at least one prescription of β-blocker oral preparations or eye-drops. The prescribed β-blockers were atenolol, carvedilol, metoprolol propranolol and timolol eye drops.

Outcome 3: Proportion of patients without check of renal function among patients aged ≥ 75 years on ACEI or loop diuretics

There were 11 patients aged ≥ 75 years with evidence of long-term (> 15 months) prescription of ACE inhibitors or loop diuretics. All patients had received a check of their renal function in the last 15 months.

Outcome 4: Proportion of oral contraceptive users among female patients with venous or arterial thromboembolism

Four female patients had venous or arterial thromboembolism. No patients were on any oral contraceptive.

Outcome 5a, 5b: Proportion of patients without full blood count or liver function test among methotrexate users

There were 14 patients with evidence of at least three months of prescribing of methotrexate. All patients had been given a full blood count or liver function test.

Outcome 6: Proportion of patients without INR among warfarin users

There were 16 patients with evidence of at least three months of prescribing of warfarin. Of the patients at risk, 25.0% had no INR recording in the previous three months.

Outcome 7: Proportion of patients without a lithium level check among lithium users

There were two patients with evidence of at least three months of prescribing of lithium. They had not had a lithium level check in the last three months.

Outcome 8: Proportion of patients without thyroid function test among amiodarone users

None of the patients was using amiodarone.

Outcome 9: Proportion of patients without instructions taken every week among methotrexate users

Fourteen patients were using methotrexate. All patients had been given instructions to take it every week.

Outcome 10: Proportions of patients receiving a dose of more than 200 mg per day among amiodarone users

None of the patients was using amiodarone.

Outcome 11: Proportion of patients with at least one prescribing problem (i.e. Outcomes 1, 2 and 4) among patients at risk of at least one prescribing problem

There were 259 "at risk" patients with at least one prescribing problem. Of the patients at risk, 10.8% had experienced at least one prescribing problem.

Outcome 12: Proportion of patients with at least one monitoring problem (i.e. Outcomes 3, 5 (a or b), 6, 7 and 8) among patients at risk of one monitoring problem

There were 43 "at risk" patients with at least one monitoring problem. Of the patients at risk, 13.95% had at least one monitoring problem.

Outcome 13: Proportion of patients prescribed an oral NSAID (excluding aspirin), without co-prescription of an ulcer-healing drug among patients aged ≥ 65 years

Two hundred and sixty-nine patients were aged ≥65 years without co-prescription of an ulcer-healing drug. Of the patients at risk, 19.3% had been given at least one prescription of an oral NSAID (except aspirin) without co-prescription of an ulcer-healing drug. The NSAIDs prescribed were diclofenac, ibuprofen and meloxicam.

Outcome 14: Proportion of patients prescribed an anti-platelet drug without co-prescription of an ulcer-healing drug among peptic ulcer patients

Four patients had a history of peptic ulcer without co-prescription of an ulcer-healing drug. Out of the patients at risk, 25.0% had been prescribed an anti-platelet drug. The anti-platelet prescribed was aspirin.

Outcome 15: Proportion of patients prescribed an oral NSAID (excluding aspirin) among warfarin or NOAC users

Thirty-two patients had been prescribed warfarin or NOAC. Out of the patients at risk, 6.25% had at least one prescription of an oral NSAID. The NSAID prescribed was meloxicam.

Outcome 16: Proportion of patients prescribed an anti-platelet drug without co-prescription of an ulcer-healing drug among warfarin or NOAC users

Twenty-two patients had been prescribed warfarin or NOAC without co-prescription of an ulcer-healing drug. Out of the patients at risk, 50.0% had been given at least one prescription of an anti-platelet drug. The anti-platelet drugs prescribed were aspirin and clopidogrel.

Outcome 17: Proportion of patients prescribed an anti-platelet drug without co-prescription of an ulcer-healing drug among aspirin users

Three hundred and forty-four patients had been prescribed aspirin without co-prescription of an ulcer-healing drug. Out of the patients at risk, 6.7% had been given at least one prescription of an anti-platelet drug. The anti-platelet drug prescribed was clopidogrel.

Outcome 18: Proportion of patients prescribed a long-acting beta-2 agonist inhaler (excluding combination products with inhaled corticosteroid) who were not also prescribed an inhaled corticosteroid among asthma patients

All patients with asthma had been prescribed a long-acting beta-2 agonist inhaler (combination products with inhaled corticosteroids).

Outcome 19: Proportion of patients prescribed an oral NSAID (excluding aspirin) among patients with heart failure

Fourteen patients had heart failure. Out of the patients at risk, 21.4% had been given at least one prescription of an oral NSAID. The NSAID prescribed was meloxicam.

Outcome 20: Proportion of patients prescribed an antipsychotic for > 6 weeks among patients aged ≥65 years with dementia but not psychosis

Seventeen patients aged ≥65 years had dementia (not psychosis). Out of the patients at risk, 11.8% had been given at least one prescription of an antipsychotic for > 6 weeks. The antipsychotics prescribed were risperidone and quetiapine.

Outcome 21: Proportion of patients prescribed an oral NSAID (excluding aspirin) among patients with eGFR < 45

There were 38 patients with eGFR < 45. Out of the patients at risk, none had at least one prescription of an oral NSAID.

The highest risk of prescribing error was in patients with asthma who had been prescribed a β-blocker. The highest monitoring error was in patients receiving lithium for at least three months who had not received a recorded check of their lithium concentrations in the previous three months.

7.3.2 Overall period prevalence rate

We found a total of 162 prescribing/monitoring errors during the study period, categorised as the following: 122 prescribing errors (contraindications), six monitoring error and 34 Composite secondary outcome measures prescribing/monitoring errors.

Overall period prevalence rate

Numerator = the number of patients experiencing one or more medication error at any time during the 15 month period = 117 patients.
Denominator = the total number of patients in the study population = 2000 patients.
The overall period prevalence of patients with at least one medication errors over 15 months= 117 (numerator)/2000 (denominator) = 5.85% (95% CI 4.8 to 6.9).

Numerator = the number of medication errors at any time during the 15 month period = 162 patients.
Denominator = the total number of patients in the study population = 2000 patients.
The overall period prevalence of medication errors over 15 months= 162 (numerator)/2000 (denominator) = 8.1% (95% CI 6.5 to 9.7).

7.3.3 Risk factors

a. Medication and patient-related risk factors

Risk factors that significantly predicted the overall patients at risk of experiencing medications errors were:

1. Patients aged ≥ 65 years. Such patients were estimated to be 27 times more likely to be at risk of experiencing medication error than those aged 18-64 years (OR 27.2; 95% CI 18.6 to 39.85)

2. Male patients were estimated to be two times more likely to be at risk of experiencing medication error than female patients (OR 1.9; 95% CI 1.5 to 2.25)

3. Saudi nationality patients were estimated to be three times more likely to be at risk of experiencing medication error than non-Saudi patients (OR 2.7; 95% CI 2.2 to 3.3)

4. Patients taking five or more drugs (polypharmacy) were estimated to be five times more likely to be at risk of experiencing medication error than those taking fewer than five drugs (OR 4.7; 95% CI 3.8 to 5.8) (Table 7-3).

	Age (≥ 65 / 18-64 years) **OR**; 95% CI	P value	**Gender** (male /female) **OR**; 95% CI	P value	**Nationality** (Saudi / non-Saudi) **OR**; 95% CI	P value	Taking five or more drugs (**Polypharmacy)** (yes/no) **OR**; 95% CI	P value	**OTC** (yes/no) **OR**; 95% CI	P value
Overall patients at risk of experiencing medications errors										
	27.2; 18.6 to 39.85	0.00	1.9; 1.5 to 2.25	0.00	2.7; 2.2 to 3.3	0.00	4.7; 3.8 to 5.8	0.00	0.8; 0.55 to 1.25	0.38
Number of individual patients at risk outcome										
1	15.7; 1.6 to 151.5	0.02	5.6; 0.6 to 54.1	0.14	1.5; 0.15 to 14.1	0.74	NA	-	NA	-
2a	4.5; 1.5 to 13.5	0.01	2.2; 0.7 to 6.5	0.16	2.7; 0.6 to 12.2	0.19	NA	-	NA	-
2b	1.5; 1.0 to 2.05	0.03	0.9; 0.7 to 1.2	0.46	1.3; 0.9 to 1.8	0.06	2.7; 2.0 to 3.7	0.00	1.4; 0.7 to 2.9	0.32
3	NA	-	1.1; 0.3 to 3.65	0.91	NA	-	3.6; 0.8 to 16.7	0.10	NA	-
4	NA	-	NA	-	NA	-	0.8; 0.1 to 5.6	0.82	NA	-

	Age (≥ 65 / 18-64 years) **OR**; 95% CI	P value	**Gender** (male /female) **OR**; 95% CI	P value	**Nationality** (Saudi / non-Saudi) **OR**; 95% CI	P value	Taking five or more drugs (**Polypharmacy)** (yes/no) **OR**; 95% CI	P value	**OTC** (yes/no) **OR**; 95% CI	P value
5a	NA	-	0.5; 0.1 to 1.8	0.29	1.8; 0.5 to 6.5	0.37	2.9; 0.8 to 10.5	0.10	NA	-
5b	NA	-	0.5; 0.1 to 1.8	0.29	1.8; 0.5 to 6.5	0.37	2.9; 0.8 to 10.5	0.10	NA	-
6	5.3; 1.9 to 14.2	0.00	1.45; 0.5 to 3.9	0.46	3.4; 0.8 to 15.2	0.10	5.6; 1.3 to 24.8	0.02	NA	-
7	NA	-	NA	-	NA	-	0.8; 0.1 to 12.7	0.87	0.05; 0.0 to 0.85	0.04
9	NA	-	0.5; 0.1 to 1.8	0.29	1.8; 0.5 to 6.5	0.37	1.9; 0.6 to 6.4	0.25	NA	-
11	1.6; 1.2 to 2.2	0.00	0.95; 0.7 to 1.25	0.74	1.4; 1.1 to 1.9	0.02	2.8; 2.1 to 3.8	0.00	1.55; 0.8 to 3.1	0.22
12	3.9; 2.1 to 7.2	0.00	0.9; 0.5 to 1.7	0.75	2.2; 0.9 to 4.7	0.05	3.55; 1.6 to 7.7	0.00	2.3; 0.3 to 16.6	0.42
13	NA	-	2.2; 1.7 to 2.9	0.00	9.9; 5.9 to 16.9	0.00	3.9; 2.8 to 5.3	0.00	0.8; 0.5 to 1.4	0.47

	Age (≥ 65 / 18-64 years) **OR**; 95% CI	P value	**Gender** (male /female) **OR**; 95% CI	P value	**Nationality** (Saudi / non-Saudi) **OR**; 95% CI	P value	Taking five or more drugs (**Polypharmacy)** (yes/no) **OR**; 95% CI	P value	**OTC** (yes/no) **OR**; 95% CI	P value
14	15.7; 1.6 to 151.5	0.02	5.6; 0.6 to 54.1	0.14	1.5; 0.15 to 14.1	0.74	NA	-	NA	-
15	6.2; 3.0 to 12.45	0.00	1.5; 0.7 to 2.95	0.29	2.7; 1.0 to 6.9	0.05	4.4; 1.7 to 11.4	0.00	1.65; 0.2 to 12.3	0.62
16	4.4; 1.9 to 10.3	0.00	1.3; 0.55 to 3.0	0.55	3.1; 0.9 to 10.6	0.07	2.7; 1.0 to 7.4	0.05	1.1; 0.1 to 8.4	0.91
17	4.7; 3.6 to 6.1	0.00	2.3; 1.8 to 2.9	0.00	2.4; 1.8 to 3.25	0.00	5.2; 3.8 to 6.9	0.00	0.6; 0.4 to 0.9	0.02
19	5.3; 1.8 to 15.2	0.00	0.5; 0.1 to 1.8	0.29	6.4; 0.8 to 49.0	0.07	NA	-	NA	-
20	NA	-	2.1; 0.8 to 5.5	0.13	NA	-	3.7; 1.1 to 13.0	0.04	0.4; 0.1 to 1.7	0.22
21	7.6; 3.9 to 14.6	0.00	1.4; 0.7 to 2.6	0.35	5.8; 1.8 to 18.9	0.00	14.7; 3.5 to 61.3	0.00	0.9; 0.2 to	0.95

	Age (≥ 65 / 18-64 years) **OR**; 95% CI	P value	**Gender** (male /female) **OR**; 95% CI	P value	**Nationality** (Saudi / non-Saudi) **OR**; 95% CI	P value	Taking five or more drugs (**Polypharmacy)** (yes/no) **OR**; 95% CI	P value	**OTC** (yes/no) **OR**; 95% CI	P value
									4.0	

Table 7-3. Cohort study association between patient and medication-related risk factors and patients at risk of error outcomes. (Data obtained from logistic regression model). NA: No association. OR = 1.

b. Physician-related risk factors

Risk factors that significantly predicted the overall patients who were at risk of experiencing medication errors were a) physician's male gender was estimated to be two times more likely to be at risk of experiencing medication error than physician's female physicians (OR 1.6; 95% CI 1.3 to 2.1) and b) Saudi nationality physicians were estimated to be two times more likely to be at risk of experiencing medication error than non-Saudi physicians (OR 1.9; 95% CI 1.5 to 2.5) (Table 7-4).

	Age (≥ 51 / 18-50 years) **OR**; 95% CI	P value	**Gender** (male /female) **OR**; 95% CI	P value	**Nationality** (Saudi / non-Saudi) **OR**; 95% CI	P value	**Certificate (**American, British, Canadian, Jordanian certified, or none) **OR**; 95% CI	P value	**Years of experience** (≥ 10 /1-9 years) **OR**; 95% CI	P value	**Number** (≥ one /one) **OR**; 95% CI	P value
Overall patients at risk of experiencing medications errors												
	1.0; 0.8 to 1.3	0.84	1.6; 1.3 to 2.1	0.00	1.9; 1.5 to 2.5	0.00	1.0; 0.9 to 1.2	0.49	1.1; 0.9 to 1.4	0.39	0.5; 0.4 to 0.6	0.00
Number of individual patients at risk outcome												
2a	0.6; 0.15 to 2.2	0.42	1.7; 0.45 to 6.55	0.42	2.85; 0.9 to 9.4	0.09	1.3; 0.7 to 2.3	0.41	1.2; 0.35 to 4.2	0.74	0.3; 0.1 to 1.1	0.08
2b	1.4; 0.9 to 1.9	0.06	1.1; 0.8 to 1.5	0.65	0.9; 0.6 to 1.3	0.59	1.05; 0.9 to 1.2	0.49	1.0; 0.75 to 1.4	0.84	1.05; 0.7 to 1.6	0.79
3	1.5; 0.4	0.54	1.1; 0.25	0.92	1.1; 0.2 to 5.6	0.88	1.0; 0.5 to 2.0	0.98	0.7; 0.2 to 2.8	0.62	0.4; 0.1 to	0.19

	Age (≥ 51 / 18-50 years) **OR**; 95% CI	P value	**Gender** (male /female) **OR**; 95% CI	P value	**Nationality** (Saudi / non-Saudi) **OR**; 95% CI	P value	**Certificate (**American, British, Canadian, Jordanian certified, or none) **OR**; 95% CI	P value	**Years of experience** (≥ 10 /1-9 years) **OR**; 95% CI	P value	**Number** (≥ one /one) **OR**; 95% CI	P value
	to 6.2		to 4.5								1.55	
4	0.8; 0.1 to 8.5	0.83	0.3; 0.0 to 3.55	0.36	NA	-	0.3; 0.05 to 2.0	0.23	0.35; 0.0 to 3.9	0.39	NA	-
5a	1.9; 0.6 to 6.1	0.31	0.4; 0.1 to 1.25	0.11	1.3; 0.3 to 4.8	0.72	0.7; 0.4 to 1.4	0.33	3.2; 0.7 to 14.8	0.14	0.6; 0.15 to 2.0	0.38
5b	1.9; 0.6 to 6.1	0.31	0.4; 0.1 to 1.25	0.11	1.3; 0.3 to 4.8	0.72	0.7; 0.4 to 1.4	0.33	3.2; 0.7 to 14.8	0.14	0.6; 0.15 to 2.0	0.38
6	0.6; 0.15 to 2.2	0.42	1.1; 0.3 to 3.9	0.85	1.3; 0.3 to 4.8	0.72	0.8; 0.4 to 1.5	0.49	1.2; 0.35 to 4.2	0.74	1.1; 0.2 to 4.8	0.92
7	NA	-	NA	-	NA	-	NA	-	NA	-	0.15; 0.0 to 2.5	0.19

	Age (≥ 51 / 18-50 years) **OR**; 95% CI	P value	**Gender** (male /female) **OR**; 95% CI	P value	**Nationality** (Saudi / non-Saudi) **OR**; 95% CI	P value	**Certificate (**American, British, Canadian, Jordanian certified, or none) **OR**; 95% CI	P value	**Years of experience** (≥ 10 /1-9 years) **OR**; 95% CI	P value	**Number** (≥ one /one) **OR**; 95% CI	P value
9	1.9; 0.6 to 6.1	0.31	0.5; 0.2 to 1.8	0.30	1.3; 0.3 to 4.8	0.72	0.7; 0.4 to 1.4	0.33	1.9; 0.5 to 7.1	0.35	0.6; 0.15 to 2.0	0.38
11	1.3; 0.9 to 1.7	0.13	1.1; 0.8 to 1.5	0.56	0.9; 0.7 to 1.4	0.83	1.0; 0.9 to 1.2	0.54	1.0; 0.7 to 1.4	0.95	0.9; 0.7 to 1.4	0.95
12	1.1; 0.5 to 2.3	0.76	0.7; 0.3 to 1.4	0.29	1.2; 0.5 to 2.7	0.69	0.7; 0.5 to 1.1	0.13	1.7; 0.8 to 3.8	0.17	0.6; 0.3 to 1.2	0.15
13	0.9; 0.7 to 1.25	0.61	2.6; 1.8 to 3.7	0.00	2.7; 1.9 to 3.7	0.00	1.1; 0.9 to 1.3	0.23	1.4; 1.0 to 1.9	0.04	0.3; 0.2 to 0.4	0.00
15	0.7; 0.3 to 1.6	0.38	1.8; 0.7 to 4.7	0.19	1.5; 0.6 to 3.7	0.38	0.8; 0.55 to 1.3	0.45	1.1; 0.5 to 2.55	0.83	0.45; 0.2 to 1.0	0.06
16	0.6; 0.2	0.41	1.6; 0.5 to	0.42	1.9; 0.6 to 5.7	0.25	0.9; 0.6 to 1.6	0.87	0.9; 0.3 to 2.7	0.91	0.4; 0.15	0.06

	Age (≥ 51 / 18-50 years) **OR**; 95% CI	P value	**Gender** (male /female) **OR**; 95% CI	P value	**Nationality** (Saudi / non-Saudi) **OR**; 95% CI	P value	**Certificate (**American, British, Canadian, Jordanian certified, or none) **OR**; 95% CI	P value	**Years of experience** (≥ 10 /1-9 years) **OR**; 95% CI	P value	**Number** (≥ one /one) **OR**; 95% CI	P value
	to 1.9		5.2								to 1.0	
17	0.9; 0.7 to 1.2	0.63	1.7; 1.3 to 2.3	0.00	1.9; 1.45 to 2.7	0.00	0.9; 0.85 to 1.1	0.78	0.9; 0.7 to 1.3	0.91	0.7; 0.5 to 0.9	0.01
19	0.7; 0.2 to 2.6	0.55	5.9; 0.7 to 46.4	0.09	5.2; 1.4 to 18.4	0.01	1.1; 0.6 to 2.0	0.79	1.6; 0.4 to 6.4	0.47	0.6; 0.15 to 2.0	0.38
20	0.8; 0.2 to 2.6	0.67	7.2; 0.9 to 55.8	0.06	1.1; 0.3 to 4.2	0.85	1.05; 0.6 to 1.8	0.86	0.3; 0.1 to 1.2	0.09	0.3; 0.1 to 0.8	0.01
21	0.8; 0.4 to 1.8	0.62	3.6; 1.2 to 10.6	0.02	2.9; 1.4 to 6.5	0.01	1.3; 0.9 to 1.9	0.16	1.9; 0.8 to 4.6	0.14	0.4; 0.2 to 0.75	0.01

Table 7-4. Cohort study association between physician-related risk factors and patients at risk of error outcomes. (Data obtained from logistic regression model). NA: No association. OR = 1.

7.4 Chapter summary

In this retrospective cohort study of adult patients from Family Medicine and Polyclinics in KFSH&RC, Riyadh, SA, clinically important errors in medicine management were found to be common in a randomly selected sample of 2000 patients' records. The overall period prevalence of patients with at least one medication error over 15 months was (5.85%; 95% CI 4.8 to 6.9). The overall period prevalence of medication errors over 15 months was (8.1%; 95% CI 6.5 to 9.7). The highest risk of prescribing error was in patients with asthma who had been prescribed a β-blocker. The highest risk of monitoring error was in patients receiving lithium for at least three months who had not received a recorded check of their lithium concentrations in the previous three months. The overall period prevalence estimate of the first 12 clinically important errors in medicine management in the cohort study was more compared to the QRESEARCH analysis of secular trends estimates. This prevalence variation may reflect the different healthcare services provided and the different method of data extraction employed in the two countries (SA and UK).

Medication and patient-related risk factors that significantly predicted the overall patients at risk of medication errors were patient's age of ≥ 65 years, male gender, Saudi nationality and taking five or more drugs (polypharmacy). Physician-related risk factors that significantly predicted the overall patients at risk of experiencing medication errors were physician's male gender and physician's Saudi nationality.

This cohort study is the first in a Saudi Arabian ambulatory care setting that has been designed to compare the period prevalence of clinically important errors in medicine management with that in another country i.e.UK.

Next chapter provides a discussion and conclusions for this study.

Chapter Eight: Discussion and Conclusions

8.1 Introduction

Patient safety is a public concern in healthcare systems across the world.(8) Medication errors and ADEs are common and are responsible for considerable patient harm.(8) Patient safety in hospital settings has been extensively studied.(2, 12, 13) In an effort to complement this, my research focused on measuring the epidemiology of medication errors and ADEs in community settings, since the latter location is where most of medication use takes place. Most of the previous studies have been conducted on elderly populations in economically-developed countries. There is therefore clearly a need to extend this work to low- and middle-income countries, particularly given the WHO's recent launch of a Global Patient Safety Challenge.(90, 91) Thus, the primary question for my research was "What is the epidemiology of medication errors, associated ADEs and risk factors for these outcomes in the community settings?". In order to address this research question, the following objectives were developed:

1. To review the literature on medication errors in community settings.
2. To estimate the incidence/period prevalence of medication errors and error-related ADEs in community settings.
3. To estimate the period prevalence of medication errors in community settings in Riyadh, SA.
4. To identify risk factors associated with medication errors and error-related ADEs.
5. To compare the QRESEARCH analysis of secular trends in the UK with the findings from my cohort in SA.

A phased programme of work was developed to achieve these objectives: Phase 1, a systematic literature review; Phase 2, a feasibility study; Phase 3, a pilot retrospective cohort study and Phase 4, a larger-scale retrospective cohort study.

For Phases 2-4, I used a list of 21 clinically important errors in medicine management (21 medication errors).(85, 107) It was considered by a panel of healthcare professionals that 13 of these errors are associated with high risk and three (Outcome 1: peptic ulcer and NSAID without ulcer-healing drug, Outcome 6: warfarin and INR and Outcome 21: eGFR < 45 and

NSAID) with extreme risk to patients.(99) Phases 2-4 focused only on the errors; not the adverse events themselves. Details of the risk and associated ADEs are described in Appendix 7.

8.2 Key research findings

There were 60 observational studies identified in Phase 1, the systematic review of the epidemiology of medication errors and error-related adverse events and their risk factors. These studies were conducted in different countries and with different populations, methods for errors detection, medication error definitions and outcome measures. The prevalence of prescribing errors was reported in 46 studies; point or period prevalence estimates ranged widely from 2.0-94.0%. Inappropriate prescribing was the most common type of error reported. Only one study reported the prevalence of monitoring errors, finding that incomplete therapeutic/safety laboratory-test monitoring occurred in 73.0% of patients. The incidence of preventable ADEs was estimated as 15/1000 person-years, the prevalence of DDI-related ADR as 7.0% and the prevalence of preventable ADE as 0.4%. A number of patient, healthcare professional and medication-related risk factors were identified, including the number of medications used by the patient, increased patient age (≥75 years), the number of multi-morbidities, use of anticoagulants, cases where more than one physician was involved in patients' care and care being provided by family the physicians/GP.

My systematic review identified important limitations and discrepancies in the methodologies used, as well as gaps in the literature on the epidemiology and outcomes of medication errors in community settings. In addition, my systematic review did not identify a validated method for detecting all classes of medication errors and was unable to find a study that investigated the incidence of medication errors. Bearing the above points in mind, and the fact that most of the preventable ADEs were as a result of prescribing errors and medication monitoring errors and following discussion with other researchers and supervisors, I identified a validated tool for measuring medication errors developed by Avery et al. (2012) in the PINCER trial consisting of a list of clinically important errors in prescribing and monitoring in primary care. The PINCER trial is one of the world's first randomised studies aiming to reduce the risk of medication errors in general practices.

The decision in Phase 2, the feasibility study, was to: a) identify the ambulatory setting and electronic database; b) test the feasibility of data extraction as well as the reliability of key outcome measures; and c) facilitate the conduct of my epidemiological research on a pre-specified list of clinically important errors in medicine management. The main findings from this phase were that I selected the EHRs of KFSH&RC Family Medicine and Polyclinics, Riyadh, SA and that the pilot phase was feasible, likely to provide random sample and all information needed for data collection was available in one electronic system and were useable in the following two phases.

Phase 3 was the pilot retrospective cohort study to pilot the research procedure and to inform sample size calculations for undertaking a larger cohort study. In this study, a random sample of 200 records was selected. Thirty-two clinically important errors in medicine management were identified. The overall period prevalence of patients with at least one medication error over 15 months was (10.0%; 95% CI 5.8 to 14.2). The overall period prevalence of medication errors over 15 months was (16.0%; 95% CI 8.2 to 23.8). Risk factors that significantly predicted the overall patients at risk of medication errors were patient's age of ≥65 years and using OTC medications.

The findings from this phase suggested that more long-term data were needed to explore further the effects of physician-related risk factors on medication errors outcomes, a goal that was accomplished with a larger-scale, retrospective cohort study.

In Phase 4, the retrospective cohort study, a random sample of 2000 records was selected, resulting in 162 clinically important errors in medicine management being identified. Therefore, the overall period prevalence of patients with at least one medication error over 15 months was (5.85%; 95% CI 4.8 to 6.9). The overall period prevalence of medication errors over 15 months was (8.1%; 95% CI 6.5 to 9.7). I obtained lower precision of estimates from my cohort study compared to the pilot study (Phase 3). Medication and patient-related risk

factors that significantly predicted the overall patients at risk of errors were patient's age of ≥ 65 years, male gender, Saudi nationality and taking five or more drugs (polypharmacy).

In both Phases 3 and 4, the highest risk of prescribing error was found to be in Outcome 2a (patients with asthma who had been prescribed a β-blocker) affecting 10 patients; three patients in Phase 3 and seven patients in Phase 4, while, for monitoring error, the highest risk was in Outcome 7 (patients receiving lithium for at least three months who had not had a recorded check of their lithium concentrations in the previous three months), affecting only three patients; one patient in Phase 3 and two patients in Phase 4. The overall period prevalence estimate of the first 12 clinically important errors in medicine management in the cohort study was more compared to the QRESEARCH analysis of secular trends estimate. This may reflect different healthcare services provided and the different method of data extraction between both countries.

The main cohort study phase results were consistent with my systematic review (Phase 1) results. Medication errors in community settings are common, particularly prescribing errors; as well as in relation to the most common risk factors seen in both phases i.e. the number of medications used by the patient and increased patient age.

8.3 Strengths and limitations

Strengths

A logical and systematic course of action has been employed in this study, which started with a systematic review and progressed from feasibility to pilot work then, my definitive larger retrospective cohort study.

Phase 1. The main strengths of this systematic review are that a rigorous and transparent process was employed, which included no language restrictions, an independent screening of titles and abstracts, independent data extraction and critical appraisal of included studies by two reviewers. The use of the International Classifications for Patient Safety (ICPS) conceptual framework,(131) which provides a comprehensive definition of each concept and type of error in the medicines' management process, is a further strength. In addition, the

systematic review is the first medication errors and error-related adverse events review located within community settings.

For Phases 2 and 3: all the required information was available in the one system and no missing data were found.

For Phase 3: firstly, this is the first epidemiological pilot study working on a pre-specified list of clinically important errors in ambulatory care in SA. Secondly, a simple random sample was applied to avoid selection bias in sampling. Lastly, independent data collection by two researchers allowed a more accurate rate of medication errors to be measured with less bias.

Phase 4. Firstly, the list of clinically important errors in prescribing and monitoring stages that were used in my study was validated and developed according to a systematic review, other research and expertise, and consensus on overall burden and severity of iatrogenic harm in primary care in the PINCER trial.(92, 101, 102) Secondly, data collection of 10% of the sample size was independently undertaken by two reviewers, resulting in substantial agreement. Thirdly, both medication and physician-related factors that contribute to the occurrence of the risk of experiencing medication errors in the cohort study were considered. Fourthly, the large, representative cohort of adults was followed up over a 15 month period. Fifthly, Outcome 5, for methotrexate, was seen more in the cohort study compared to the pilot study. This could be due to the greater sample size and the higher rate of patients having rheumatoid arthritis, psoriasis or psoriatic arthritis. Lastly, it should be noted that this is the first epidemiological cohort study working on a pre-specified list of clinically important errors in ambulatory care in SA.

Limitations

The Saudi healthcare system has a variety of limitations that result in challenges to its system when located in the community. Medication use and monitoring in the community care context, where the actual medication use takes place, is not controlled or restricted and a number of prescription medications are available as OTC drugs; the exception being narcotics, psychotropic substances and antibiotics, antibiotics were recently added by the MOH.(67) As a result, current patient medication lists may be missing. In addition, there is a

lack of a unified electronic national health information system and limited use of computerised provider order entry. Furthermore, the concept of medication safety is still new.(78)

Phase 1. Firstly, despite the thorough process, no data were found regarding the dispensing error stage. This might be due to the lack of a 'dispensing error' key-term in our search strategy, although 'medication therapy management' as a key-term was included. However, 10 studies on dispensing errors were excluded because they failed to satisfy the inclusion criteria on one or more counts. Secondly, no data were found regarding the administration error stage. However, 14 studies on administration errors were also excluded for the same previous reason; the studies failed to meet the inclusion criteria. Thirdly, this systematic review had different outcomes reported in a variety of ways using different tools and methodologies that made combining results into meta-analysis difficult. Lastly, the studies addressed risk factors adjusted for different confounders, which made it difficult to generate comparable estimates and/or make causal inferences about whether the harm resulted from the medication error.

Phase 2. Firstly, all the outcomes were seen at least once in a total of 500 patients except for Outcomes number 7, 8 and 10 involving amiodarone and lithium. Although amiodarone and lithium were not restricted to a specific specialist, none of the patients were on lithium, which could be because more cases are seen in psychiatric clinics and/or the rate of bipolar disorder in our studied population was low. In addition, none of the patients were on amiodarone, and that could be because the majority of atrial fibrillation patients are seen in the cardiology clinic and amiodarone is rarely prescribed. It was concluded there was a low prescribing rate of amiodarone to cardiac arrhythmia patients.

Phase 3. Firstly, this was an observational study conducted using a retrospective study design with a small sample size, the OR estimates had wide 95% CI, and, as a result, the estimates obtained should be interpreted with caution. Secondly, due to the different rate of disease in the studied populations, Outcome 5 and 9 (methotrexate) was not seen, this could be due to the low rate of patients having rheumatoid arthritis and the low number of patients on methotrexate who were visiting the Family Medicine and Polyclinics. Lastly, maximum likelihood estimation of the logistic regression model in the pilot study suffers from small

sample bias; because of the rare events, i.e. the number of events in some of the patients at risk outcomes (denominator) is small.(132)

For Phases 3 and 4: firstly, manual data collection was carried out because of the lack of technical capacity to ensure accuracy and quality of data. Manual data collection was also employed in order to avoid the delay that would be necessary for generating the required anonymised data electronically from the electronic medical records department in KFSH&RC. Secondly, documentation bias may occur within the retrospective review because the investigator must rely on information provided only in the electronic records to identify or assess the outcome. Selection bias is a particular problem with retrospective cohort studies, such as the one in this research, where exposure and outcomes have already occurred at the time of subject enrolment. Thirdly, I focused only on medication errors, excluding the associated adverse events, because of the limited research team and time period available to accomplish this PhD research. Fourthly, the most common non-prescribed medications were acetaminophen, ascorbic acid, cetirizine HCl, calcium carbonate, ferrous gluconate, folic acid, ibuprofen, loratadine, omeprazole, pseudoephedrine and ranitidine, their actual rate used by the patients might not be known because high number of OTC medications can be brought in from outside the hospital and may not be recorded by the physicians. Fifthly, due to the different rates of disease in the studied populations, Outcomes 8 and 10 (amiodarone), were not seen. That lack of cases could be because of the low prescribing rate of amiodarone to cardiac arrhythmia patients. Lastly, patients visiting the Family Medicine and Polyclinics may not be representative of the ambulatory population of SA. It was not possible formally to assess this point because Saudi national data are not available to enable comparisons between the baseline characteristics of the sample population and the whole population and the results may not be generalisable because this study was performed in a single ambulatory care context in SA.

For Phase 4: there is inconsistent type of precisions between my cohort period prevalence proportion (i.e. 95% CI) and QRESEARCH analysis of secular trends period prevalence proportion (i.e. IQR), that resulted me in comparing the proportions only without precisions.

8.4 Interpretation of findings in light of the existing literature

In Phase 1, the systematic literature review, the definitional variation issue was supported by another two reviews.(133, 134) Other systematic reviews focusing on the safety of primary care contexts identified studies with vastly different prevalence estimates of the rates of medication errors. This reflected differences in definitions, sampling strategy and the types of populations studied; the previous reviews had not investigated the risk factors for medication errors.(135, 136)

In Phase 3**,** the pilot retrospective cohort study, Akbarov et al. (2015) in a cross-sectional study using linked records in the UK general practices, used 22 medication safety indicators (18 prescribing indicators with an overall prevalence as 5.45% and 4 monitoring indicators with an overall prevalence as 7.65%).(137) In order to compare my study results with the findings from the research by Akbarov et al. (2015) study, it is important to have a consistent definition of numerator and denominator. Only 13 consistent indicators can be compared with my outcome measures. The other nine indicators were not used in my study, so a comparison between my overall outcome measures' estimate and the Akbarov et al. (2015) study overall outcome measures' estimates cannot be made. This research found higher period prevalence estimates for the following:

Outcomes 2b (asthma and β-blocker)

Outcome 13 (aged≥ 65 years using NSAID without an ulcer-healing drug)

Outcome 19 (heart failure and NSAID).

In this pilot study, I could not estimate rates for the following outcomes, because there were no events:

Outcome 1 (peptic ulcer and NSAID without an ulcer-healing drug)

Outcome 3 (ACE inhibitor / diuretics and lab test)

Outcome 4 (venous or arterial thromboembolism and arterial thrombosis and combined oral contraceptives)

Outcome 6 (warfarin and INR)

Outcome 15 (warfarin/ NOAC and NSAID)

Outcome 21 (eGFR < 45 and NSAID).

For Outcome 8 (amiodarone and thyroid function test), no patient in this study was on amiodarone. For Outcome 18 (long-acting beta-2 agonist inhaler [excluding combination products with inhaled corticosteroid] to a patient with asthma who is not also prescribed an inhaled corticosteroid), all the study's patients were on combination products with inhaled corticosteroid.

In Phase 4, the retrospective cohort study, the results of the PINCER trial cannot be directly compared to the cohort study, because the PINCER trial is an interventional study. However, it is possible to compare my research results with the QRESEARCH analysis of secular trends i.e. the large national QRESEARCH general practice database.(129)

The overall period prevalence of the first 12 clinically important errors in medicine management estimate was (3.4%; 95% CI 2.2 to 4.6) in this research compared with 0.9% for the QRESEARCH analysis of secular trends.(129) The distribution of each estimate for the outcome measures was as follow:

In my study, higher period prevalence estimates were found for:

Outcomes 2a and 2b (asthma and β-blocker)

Outcome 6 (warfarin and INR)

Outcome 7 (lithium and lithium level)

Outcome 11 (at least one prescription error)

Outcome 12 (at least one monitoring error)

In my study, I could not estimate rates for the following outcomes, because there were no events:

Outcome 1 (peptic ulcer and NSAID without an ulcer-healing drug)

Outcome 3 (ACE inhibitor / diuretics and lab test)

Outcome 4 (venous or arterial thromboembolism and arterial thrombosis and combined oral contraceptives)

Outcomes 5a and 5b (methotrexate and full blood count and methotrexate and liver function test).

For (Outcome 8: amiodarone and thyroid function test) and (Outcome 10: amiodarone dose) there was no patient on amiodarone. This may reflect both the differences in healthcare services provided in both countries and the varied methods of extracting data and outcomes employed in the two studies. In the QRESEARCH data were collected prospectively through a computer-recorded method and the level of accuracy and completeness was shown to be high.(129, 138) While in my study, the data were collected retrospectively through manual data extraction methods.

8.5 Implications for policy, practice and research

As mentioned in Chapter 2, there are several challenges and limitations in the Saudi healthcare system generally and in the community care specifically. The uncontrolled and non-restricted use of medications resulted in an increase in the number of concurrent medications used by the patients, which may have increased the risk of medication errors identified in my cohort study. Improving healthcare services and quality standards could potentially be achieved through healthcare organisation leaders and policymakers in SA building a unified national electronic health information system. Such an initiative will help facilitate medication restriction and fill the communication gaps between the healthcare settings in SA.

For healthcare professionals there is a need for a) training, education and monitoring with the involvement of specialised medication safety pharmacists in the community; b) increase the implementation of computerised prescribing with an integration of software to detect such clinically important errors in medicine management during prescription entry;(139, 140) c)

providing a record of current medication lists for each patient in the community; d) empowering and educating the patients and the public, particularly those with chronic diseases and those taking five or more drugs (polypharmacy), in order to increase their knowledge of medication safety; and e) encourage the reporting of medication errors, administration errors and dispensing errors, particularly in the community settings where there is a lack of reporting such outcomes.(90)

For patients in community settings (hence, compared to inpatient settings, patients in the community settings play a more active role in administering and managing their medications), there is a need to use tools and technology, particularly for monitoring and follow-up where most medication errors happen in this stage because of irregular outpatient visits and to show the current medication list for each pharmacy visit.

These three initiatives would improve the medical and pharmaceutical services provided for adults resulting in a safer environment in which the community can safely self-care.

As explained in the systematic review, this research has identified important limitations and discrepancies in the methodology used to study medication errors and error-related adverse drug events in community settings. There is a need for improvement in the quality of research in this area. Researchers should use a more consistent set of definitions or internationally accepted terminology and definitions of key concepts and should use a standardised set of outcome measures of medication errors in order to facilitate collation and synthesis of data. An example of definitions that could be used for medication error outcomes is the ICPS.(131) More research is needed in the areas of incidence of medication errors, administration and dispensing errors and reporting.

The findings in this cohort study have identified a high prevalence of medication errors among adults in the community settings in Riyadh. This evidence can provide baseline data for the patient safety authorities in SA. In order to increase the generalisability of my study's findings, it is important that this work is now extended by building a programme of research and continuing with multicentre cohort studies in different ambulatory care contexts in Riyadh, such as King Khalid University Hospital as well as in other Saudi regions.

Thus, a number of follow-on cohort studies are required in SA. If the high prevalence of medication errors is confirmed, relevant patient safety authorities should undertake action by planning to create and implement preventive strategies which should then be evaluated to see if they can help to reduce the risk of these medication errors.

By creating such an initiative, more information will be collected and a complete picture of medication error prevalence in the country can be formed.

These findings need to be considered in the context of designing future research related to medication safety; thereby strengthening the quality of research and improve the development of strategies to detect and prevent these errors.

8.6 Conclusions

In the area of medication errors, previous research studies have examined the prevalence of medication errors, incidence/prevalence of ADEs and associated risk factors with inconsistent outcomes and results. In SA, this topic has not received the attention it warrants. To my knowledge, the prevalence of medication errors in community settings has not been examined before. Given the dearth of studies looking at medication errors in the community globally and the global and particular shift in SA from secondary and tertiary care to community-based care, the focus of this PhD research is important and timely. The epidemiology of clinically important errors in medicines management in SA has been investigated. It is the first comprehensive in-depth studies researching medication errors in community settings in Riyadh, SA. This study shows that clinically important medication errors are common with a period prevalence estimate of 8.1% and could have the potential to harm patients. Patient-related risk factors that significantly predicted overall patients who were at risk of experiencing medication errors were age of ≥ 65 years, male gender, Saudi nationality, and taking five or more drugs (polypharmacy). Physician-related risk factors that significantly predicted the overall patients at risk of errors were physician's male gender and physician's Saudi nationality.

Healthcare professional education, recruiting physicians and clinical pharmacists who are specialised in the detection and prevention of medication errors, finding safer medications or integration of software to detect such clinically important errors in medicine management

during prescription entry, could improve the medical services provided for adult patients in SA and beyond.

Future research needs to replicate these findings in different ambulatory care contexts in SA, to explore further the error-related adverse events and to develop and evaluate interventions aimed at reducing the risk of clinically important errors in medicine management in community settings in SA.

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Appendices

Appendix 1: Terminology and definitions

Adverse drug event (ADE): Definition of Bates DW et al., an "injury resulting from medical intervention related to a drug".(5) ADEs are caused by medication errors.

Bias: "*Systematic deviation of results or inferences from truth*".(106)

Case control study: *"(Synonym: case comparison study, case compeer study, case history study, case referent study, retrospective study). The observational epidemiologic study of persons with the disease (or other outcome variable) of interest and a suitable control (comparison, reference) group of persons without the disease*".(106)

Cohort study: "***(****Synonym: concurrent, follow-up study, incidence, longitudinal, panel, prospective study) The analytic epidemiological study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed—or exposed in different degrees—to a factor or factors hypothesized to influence the occurrence of a given outcome*".(106)

Confidence Interval (CI): "*The computed interval with a given probability, e.g., 95%, that the true value of a variable such as a mean, proportion, or rate is contained within the interval".*(141)

Content validity: "*The extent to which the measurement incorporates the domain of the phenomenon under study".*(106)

Cross-sectional study: "*(Synonym: disease frequency survey, prevalence study) A study that examines the relationship between diseases (or other health outcomes) and other variables of interest as they exist in a defined population at one particular time. The presence or absence of disease and the presence or absence of the other variables (or, if they are quantitative,*

their level) are determined in each member of the study population or in a representative sample at one particular time".(106)

Descriptive study: "*A study concerned with and designed only to describe the existing distribution of variables without much regard to causal relationships or other hypotheses"*.(106)

Follow-up: "*Observation over a period of time of an individual, group, or an initially defined population whose relevant characteristics have been assessed in order to observe changes in health status or health-related variables*".(106)

Harm: "*Impairment of the physical, emotional, or psychological function or structure of the body and pain or injury resulting therefrom"*. (NCC-MERP)

Heterogeneity: "*In a meta-analysis, the variability in the intervention effects being evaluated in the different studies. It may be a consequence of clinical diversity (sometimes called clinical heterogeneity) or of methodological diversity (methodological heterogeneity), or both, among the studies*".(106)

Home setting: This is setting for which care is provided or individuals live in which a person is not considered an inpatient in a hospital.

High-alert medications: "*High-alert medications are drugs that bear a heightened risk of causing significant patient harm when used in error. Although mistakes may or may not be more common with these drugs, the consequences of an error are clearly more devastating to patients*".(32)

Imputation: "*The process of replacing some missing values in a large-scale epidemiological or social research study, when all other relevant parameters and values are known for an individual, by inserting an average or other plausible value. The process may be subject to biases and errors, and must be disclosed in reporting the results*".(106)

Incidence: *"(Synonym: incidence number) the number of new health-related events in a*

defined population within a specified period of time. It may be measured as a frequency count, a rate, or a proportion".(106)

Kappa index: "*a measure of the degree of nonrandom agreement between observers or measurements of the same categorical variable. Kappa coefficients are measures of correlation between categorical variables often used as reliability or validity coefficients".*(106)

Logistic model: "*(logistic regression model) A statistical model for the probability that a binary variable Y equals 1 as a function of a covariate x, typically used when Y is an individual's disease indicator and x is the value of a risk factor or risk indicator*".(106)

Meta-analysis: "*A statistical analysis of results from separate studies, examining sources of differences in results among studies, and leading to a quantitative summary of the results if the results are judged sufficiently similar or consistent to support such synthesis"*.(106)

Narrow therapeutic index (NTI-drugs): "*Drugs with narrow therapeutic index (NTI-drugs) are drugs with small differences between therapeutic and toxic doses*".(33)

Non-prescription drugs: Medicines that can be sold legally without a drug prescription.

Odds ratio (OR): "*(Synonym: cross-product ratio, relative odds) the ratio of two odds. The term odds is defined differently according to the situation under discussion*".(106)

Outcome: "*The result of interest in a study or experiment. A component of a participants clinical and functional status after an intervention has been applied, that is used to assess the effectiveness of an intervention*".(142)

Over-the-counter (OTC) drug: The Food and Drug Administration FDA defines OTC dr*ugs as "drugs that have been found to be safe and appropriate for use without the supervision of a health care professional such as a physician, and they can be purchased by consumers without a prescription*".(68)

Period prevalence: "*the proportion of individuals with the condition at any time during a specified time period or interval*".(106)

Pilot study: *"A small-scale test of the methods and procedures to be used on a larger scale if the pilot study demonstrates that these methods and procedures can work".*(106)

Population: "*In sampling, the whole collection of units (the "universe") from which a sample may be drawn; not necessarily a population of persons—the units may be institutions, records, or events. The sample is intended to give results that are representative of the whole population; it may deviate from that goal owing to random and systematic errors*".(106)

Prescription drug: Drugs that cannot be sold legally without a prescription.

Prevalence: "*The total number of individuals who have the condition (e.g., disease, exposure, attribute) at a particular time (or during a particular period) divided by the population at risk of having the condition at that time or midway through the period*".(106)

Probability sample: "*a sample in which the probability of each subject in the parent population being included in the sample is known*"(143)

Prospective study: "*In evaluations of the effects of healthcare interventions, a study in which people are identified according to current risk status or exposure, and followed forwards through time to observe outcome*".(142)

Protocol: "*The plan or set of steps to be followed in a study".*(106, 142) *"A Protocol for a systematic review should describe the rationale for the review, the objectives, and the methods that will be used to locate, select, and critically appraise studies, and to collect and analyse data from the included studies*".(142)

Reliability: "*a measurement is reliable when it is stable; i.e. when repetition of an experiment or measurement gives the same results*".(106)

Relative risk: "*The ratio of the RISK of disease or death among the exposed to the risk among the unexposed; this usage is synonymous with RISK RATIO*".(141)

Retrospective study: "*A study in which the outcomes have occurred to the participants before the study commenced. Case- Control studies are usually retrospective, cohort studies sometimes are, randomised controlled trials never are*".(142)

Risk factor: "*(Synonym: determinant) a factor that is causally related to a change in the risk of a relevant health process, outcome, or condition*".(106)

Sample: "*A selected subset of a population. A sample may be random or nonrandom and may be representative or non-representative*".(106)

Simple random sampling: is one type of the probability or (random) sampling defined as: "*each person has an equal chance of being selected out of the entire population*".(106)

Systematic sample: "*The procedure of selecting according to some simple, systematic rule, such as all persons whose names begin with specified alphabetic letters, born on certain dates, or located at specified points on a master list*".(106)

Search strategy: "*The combination of terms used to identify studies in an electronic database such as: MEDLINE*".(142)

Standard deviation: "*A measure of dispersion or variation. It is the most widely used measure of dispersion of a frequency distribution. It is equal to the positive square root of the variance. The mean tells where the values for a group or for an estimator are centered in terms of the overall mass of their distribution. The standard deviation is a summary of how widely dispersed the values are around this center*".(106)

Statistics: "*The science of collecting, summarising, analysing data. Data may or may be not subject to random variation"*.(106)

STATA (version14): Data analysis and statistical software.

Systematic review: "*A review of the scientific evidence, which applies strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on the specific topic. Systematic reviews differ from traditional narrative reviews, which tend to be mainly descriptive, do not involve a systematic search of the literature, and thus can suffer from selection bias*".(106)

Validity: "*An expression of the degree to which a measurement measures what it purports to measure*".(106)

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Appendix 3: Systematic review protocol

BMJ Open

Investigating the epidemiology of medication errors and error-related adverse drug events (ADEs) in primary care, ambulatory care and home settings: a systematic review protocol

Ghadah Asaad Assiri,[1,2] Liz Grant,[1] Hisham Aljadhey,[2] Aziz Sheikh[3]

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ABSTRACT

Introduction: There is a need to better understand the epidemiology of medication errors and error-related adverse events in community care contexts.

Methods and analysis: We will systematically search the following databases: Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, Eastern Mediterranean Regional Office of the WHO (EMRO), MEDLINE, PsycINFO and Web of Science. In addition, we will search Google Scholar and contact an international panel of experts to search for unpublished and in progress work. The searches will cover the time period January 1990–December 2015 and will yield data on the incidence or prevalence of and risk factors for medication errors and error-related adverse drug events in adults living in community settings (ie, primary care, ambulatory and home). Study quality will be assessed using the Critical Appraisal Skills Program quality assessment tool for cohort and case–control studies, and cross-sectional studies will be assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Descriptive Studies. Meta-analyses will be undertaken using random-effects modelling using STATA (V.14) statistical software.

Ethics and dissemination: This protocol will be registered with PROSPERO, an international prospective register of systematic reviews, and the systematic review will be reported in the peer-reviewed literature using Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

INTRODUCTION

Patient safety is a public concern in healthcare systems across the world.[1] The National Coordinating Council for Medication Error Reporting and Prevention defines a medication error as 'any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the healthcare professional, patient or consumer'.[2] Medication errors are therefore any mistakes at any stage of medication management. Adverse drug event (ADE), on the other hand, is 'an injury resulting from medical intervention related to a drug', regardless of whether an error has occurred.[3] While almost all medication errors can be prevented, ADEs can be categorised as preventable and non-preventable.[1] Box 1 provides definitions of the key terms employed in this systematic review protocol.

Medication errors and error-related ADEs are common and are responsible for considerable patient harm.[1] More specifically, ADEs can lead to morbidity, hospitalisation, increased healthcare costs and, in some cases, death.[4] It has been estimated that 5–6% of all hospitalisations are drug-related.[5 6] With estimates suggesting that ADEs causing hospital admission occur in around 10% of inpatients; approximately half of these ADEs are believed to be preventable.[7]

The cost of drug-related morbidity and mortality was estimated to be $177.4 billion annually in 2001 in the USA alone.[8]

Medication errors and ADEs are a major problem in all care settings, including home, ambulatory and community settings.[1] Children and adults who suffer from multiple long-term conditions with associated complex drug regimens are particularly at risk.[9–11]

Systematic reviews focusing on the safety of primary care contexts only have identified studies with vastly different prevalence estimates of the rates of medication errors, these reflect differences in definitions, sampling strategy and populations studied; none of these have investigated the risk factors for medication errors.[12 13]

Since the release of *To Err is Human: Building a Safer Health System* by the Institute of Medicine,[14] which focused on acute care settings, most patient safety research has

Box 1 Key definitions

- *Adverse drug event (ADE)*: Bates *et al*[3] define ADE as 'an injury resulting from medical intervention related to a drug'. Some ADEs are caused by underlying medication errors.
- *Medication error*: The National Coordinating Council for Medication Error Reporting and Prevention defines a medication error as: 'any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures and systems, including prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use'.[2] Medication errors can result from any step of the medication-use process: selection and procurement, storage, ordering and transcribing, preparing and dispensing, administration or monitoring.[1]
- *Non-prescription drugs*: Medicines that can be sold legally without a drug prescription.
- *Over-the-counter (OTC) drug*: The Food and Drug Administration defines OTC drugs as 'drugs that have been found to be safe and appropriate for use without the supervision of a healthcare professional such as a physician, and they can be purchased by consumers without a prescription'.[24]
- *Prescription drug*: Drugs that cannot be sold legally without a prescription.

been carried out on hospitalised patients.[15 16] Given that patients are increasingly managed in primary, ambulatory and home settings, there is a need to also focus attention on community care contexts.

Prior to undertaking further primary work in this area, it is important to take stock of the current evidence base, reflect on the quality of the evidence, distil key findings that have the potential to provide both estimates on the frequency of medication errors and error-related ADEs, and understand the factors underpinning this important source of preventable harm. We will therefore undertake a systematic review investigating the incidence and prevalence of and risk factors for medication errors and error-related ADEs in community (ie, primary care, ambulatory and home) settings.

Research question

What are the incidence and prevalence of and risk factors for medication errors and error-related ADEs in primary care, ambulatory care and home settings?

METHODS

Design

We will undertake a systematic review and, if possible, a meta-analysis.

Inclusion criteria

Eligibility criteria

Type of studies

Population-based cross-sectional and cohort studies will be eligible to estimate the incidence and prevalence of medication errors and ADEs; these study designs and case–control studies will be eligible to study risk factors for the development of error-related ADEs.

Population

The population of interest will be adults (≥18 years) who are dwelling in the community and living in their own homes without home healthcare or nursing at home. These patients may be self-managing, receiving care in primary care and ambulatory settings or any combination of the above.

Exposures

The exposure of interest is prescribed and/or over-the-counter medications.

Outcomes

The outcomes of interest are the incidence and prevalence of medication errors and ADEs, and risk factors for the development of medication errors and error-related ADEs. These errors may have occurred anywhere in the medicines' management process.[1] We will work with the definitions of medication errors and error-related ADEs employed in individual studies.

Exclusion criteria

1. Studies on illegal substance abuse, herbal products, home healthcare (ie, continuous medical and/or nursing care provided to patients in their own homes), nursing home, hospitalised in-patients or those managed in emergency department settings.
2. Paediatrics (<18 years).
3. Randomised controlled trials since these cannot be used to reliably assess the incidence and/or prevalence of the outcomes of interest.
4. Existing reviews since the focus is on the primary literature.
5. Studies focusing on specific medication errors or subgroups of populations.
6. Incompletely reported studies, for example, in the form of abstracts.

Search strategy

We will search the following biomedical databases for published research studies: Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, Eastern Mediterranean Regional Office of the WHO (EMRO), MEDLINE, PsycINFO and Web of Science. These databases will be searched from January 1990 to December 2015; the start date has been chosen to reflect the time when patient safety came into the consciousness of policymakers, professionals and the public.[17] In addition, we will search Google Scholar and contact an international panel of experts to search for unpublished and in progress work. The corresponding author of the eligible articles may be contacted if additional information is needed. The reference list of previous studies will be scrutinised for additional possible

eligible studies. No restriction on the language of publication will be employed.

Detailed search strategies are presented in online supplementary appendix 1.

Study selection

GA will search the databases. GA and a second reviewer will then independently screen the titles and abstracts for eligible studies according to the above detailed selection criteria. Full-text articles will be retrieved from selected studies and will be reviewed according to the selection criteria. Disagreements will be resolved by discussion between the reviewers or arbitration by a third reviewer if a decision cannot be reached. Each copy of the selected studies will be retrieved and the reason for excluding other studies will be clearly noted.

Quality assessment

The risk of bias assessments will be independently carried out on each study by two reviewers using the Critical Appraisal Skills Program quality assessment tool for cohort and case–control studies,[18] and cross-sectional studies will be assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Descriptive Studies.[19] Any disagreements will be resolved by consensus or arbitration by a third reviewer if a decision cannot be reached. Each study will be graded as being at high, medium or low risk of bias.

Data extraction

Data will be extracted by two reviewers and recorded onto a customised data extraction sheet. Discrepancies will be resolved by discussion. The following information will be extracted:

1. Author, year;
2. Study design, study type (retrospective, prospective);
3. Population of interest;
4. Exposure of interest;
5. Outcomes of interest;
6. Main findings;
7. Conclusions;
8. Additional notes.

Data analysis

Data will be summarised in detailed data tables, which will include information on the incidence, prevalence, and relative risk and ORs, together with 95% CIs, for each study (where available). STATA (V.14) statistical software will be used to pool study data if this is considered both clinically and statistically appropriate. Meta-analyses will be undertaken using random-effects modelling.[20]

Sensitivity analyses will be undertaken by excluding studies judged to be at the highest risk of bias.

Subgroup analyses will be undertaken comparing: adults (18–64 years) versus elderly (≥65 years) patients; and those who have recently been an inpatient or had a hospital visit (<30 days) versus those who have not had a recent hospital attendance (≥30 days).

If possible, funnel plots will be used to assess the presence of publication bias.[21]

Registration and reporting

This systematic review will be registered with PROSPERO, an international prospective register of systematic reviews, and will be reported using Preferred Reporting Items for Systematic Reviews and Meta-Analyses[22] and Meta-analysis Of Observational Studies in Epidemiology guidelines.[23]

DISCUSSION

This systematic review will provide a comprehensive assessment of the epidemiology of medication errors and error-related ADEs in community settings. We anticipate reporting the findings from this study in the autumn of 2016.

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Appendix 4: Systematic review level 1 ethics

Level 1 ethical application form

University of Edinburgh,

Centre for Population Health Sciences

RESEARCH ETHICS SUBGROUP

Self-Audit Checklist for Level 1 Ethical Review for PGR projects

See **Intra** website for further information:
http://www.cphs.mvm.ed.ac.uk/intra/research/ethicalReview.php

NOTE to student: *Completion of this form should be under the **oversight** of your supervisor. A good strategy would be to complete a draft as best you can, then discuss with your supervisor before completing a final copy for your supervisor to sign.*

1. **Bringing the University into disrepute**

Proposed Project *(State research question and topic area, and briefly describe method/ data. Specify also countries in which data will be collected.):*

Title : Investigating the Epidemiology of Medication Errors and Error-Related Adverse Drug Events (ADEs) in Primary Care, Ambulatory Care and Home Settings: A Systematic Review Protocol

Review question/Objective: what is the incidence/prevalence of and risk factors for medication errors and error-related ADEs in community (i.e. primary care, ambulatory and home) settings.

Patient safety is a public concern in healthcare systems across the world. The National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP) defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the health care professional, patient, or consumer. Medication errors are therefore any mistakes at any stage of the medication use process. Adverse drug events (ADEs) on the other hand are the result of an injury to a drug-related intervention, regardless of whether an error has occurred.

Prior to undertaking further primary work in this area, it is important to take stock of the current evidence base, reflect on the quality of the evidence, distil key findings that have the potential to provide both estimates on the frequency of medication errors and error-related ADEs, and understand the factors underpinning this important source of preventable harm. I am therefore undertaking a systematic review investigating the incidence and prevalence of and risk factors for medication errors and error-related ADEs in community (i.e. primary care, ambulatory and home) settings.

I will perform a systematic review on the incidence and prevalence of medication errors and error related ADEs including prescribed and non-prescribed medications (over the counter medication) in community (i.e. primary care, ambulatory and home) settings using the following databases: MEDLINE, CINAHL, EMBASE, PsycINFO, EMRO (IMEMR), Google Scholar and Web of science. Experts in the field will be contacted. Search will be done on human studies only, from 1990 until Oct 2015 and including studies globally. Excluding studies on illegal substance abuse, herbal products, home health care, nursing home, any supported home care, hospitalised in-patients or those managed in ED settings, and paediatrics (<18 years) will be excluded.

Is there any aspect of the proposed research which might bring the University into disrepute? **NO**

2. **Data protection and consent**

Are there any issues of DATA PROTECTION or CONSENT which are NOT adequately dealt with via established procedures? **NO**

These include well-established sets of undertakings. For example, a 'No' answer is justified *only if*:

(a) There is compliance with the University of Edinburgh's Data Protection procedures (see www.recordsmanagement.ed.ac.uk);

(b) Respondents give consent regarding the collection, storage and, if appropriate, archiving and destruction of data;

(c) Identifying information (e.g. consent forms) is held separately from data;

(d) There is Caldicott Guardian approval for (or approval will be obtained prior to) obtaining/ analysing NHS patient-data.

(e) There are no other special issues arising about confidentiality/consent.

3. Study participants

Will a study researcher be in direct contact with participants to collect data, whether face-to-face, or by telephone, electronic means or post, or by observation? (eg interviews, focus groups, questionnaires, assessments) **NO**

4. Duty to disseminate research findings

Are there issues which will prevent all relevant stakeholders having access to a clear, understandable and accurate summary of the research findings if they wish?* **NO**

** If, and only if, you answered 'yes' to 3 above, 'stakeholders' includes participants in the research*

5. Moral issues and Researcher/Institutional Conflicts of Interest

Are there any SPECIAL MORAL ISSUES/CONFLICTS OF INTEREST? **NO**

(a) An example of conflict of interest for a researcher would be a financial or non-financial benefit for him/herself or for a relative of friend.

(b) Particular moral issues or concerns could arise, for example where the purposes of research are concealed, where respondents are unable to provide informed consent, or where research findings could impinge negatively/ differentially upon the interests of participants.

(c) Where there is a dual relationship between researcher and participant (eg where research is undertaken by practitioners so that the participant might be unclear as to the distinction between 'care' and research)

6. **Potential physical or psychological harm, discomfort or stress**

(a) Is there a FORSEEABLE POTENTIAL for PSYCHOLOGICAL HARM or STRESS for participants? **NO**

(b) Is there a FORSEEABLE POTENTIAL for PHYSICAL HARM or DISCOMFORT for participants? **NO**

(c) Is there a FORSEEABLE RISK to the researcher? **NO**

Examples of issues/ topics that have the potential to cause psychological harm, discomfort or distress and should lead you to answer 'yes' to this question include, but are not limited to:

relationship breakdown; bullying; bereavement; mental health difficulties; trauma / PTSD; violence or sexual violence; physical, sexual or emotional abuse in either children or adults.

7. **Vulnerable participants**

Are any of the participants or interviewees in the research considered to be vulnerable? e.g. children and young people under age of 16, people who are in custody or care, marginalised/stigmatised groups **NO**

8**. Protection of research subject confidentiality**

Are there any issues of CONFIDENTIALITY which are NOT adequately handled by normal tenets of confidentiality for academic research? **NO**

These include well-established sets of undertakings that should be agreed with collaborating and participating individuals/organisations. For example, a 'No' answer is justified *only if*:

(a) There will be no attribution of individual responses;

(b) Individuals (and, where appropriate, organisations) are anonymised in stored data, publications and presentation;

(c) There has been specific agreement with respondents regarding feedback to collaborators and publication.

Overall assessment

- If every answer above is a definite NO, the self-audit has been conducted and confirms the ***ABSENCE OF REASONABLY FORESEEABLE ETHICAL RISKS*** *– please tick box*

  X

  This means that regarding this study, as currently self-audited, no further ethical review actions are required within CPHS. However, if in the coming weeks/months there is any change to the research plan envisaged now (and outlined above), the study should be ***re-audited*** *against a Level 1 form, because it may be that the change made negates the absence of ethical risks signed off here.*

- If one or more answers are YES, then risks have been identified and prior to commencing any data collection **formal ethical review** is required - either:
  - ~ by NHS REC (NB copy of ethics application and decision letter to be sent to CPHS Ethics); or
  - ~ if not to be formally reviewed by NHS REC, then CPHS level 2/3 ethical review required. *[If either of 5 or 7 are answered 'yes' then almost certainly level 3 is required.]*

Two copies of this form should be taken for inclusion in the final dissertation and the original should be returned to the CPHS Ethics administrator.

Ghadah Asaad Assiri Professor Aziz Sheikh

Student Name Supervisor Name

Student Signature Supervisor Signature *****

*** NOTE to supervisor:** *The CPHS Ethics Subgroup will not check this form (the light touch Level 1 form means we have insufficient detail to do so). By counter-signing this check-list as truly warranting all 'No' answers,* ***you*** *are taking responsibility, on behalf of CPHS and UoE, that the research proposed truly poses no potential ethical risks. Therefore, if there is any doubt on any issue, it would be a wise precaution to mark it as 'uncertain' and contact the Ethics Subgroup as to whether a level 2 form might be required as well. (See Intra Ethics website – URL at top of form).*

Appendix 5: Description of databases definitions

CINAHL: The Cumulative Index to Nursing and Allied Health. "*References and abstracts on nursing, biomedical, allied health and consumer health literature. Also includes health care books, nursing dissertations, selected conference proceedings, standards of practice, educational software, audiovisuals and book chapters, as well as Evidence-Based care sheets. Coverage: 1982-present*".(144)

EMBASE: "*Bibliographic database which gives access to online version of Excerpta Medica. It is produced by Elsevier Science Publishers B.V. and offers international coverage of the drug-related literature (drugs and toxicology, clinical medicine, biotechnology and bioengineering, health affairs, psychiatry, forensic medicine. The database includes data from 3500 biomedical journals, dating back to 1974. It is updated monthly*".(145)

EMRO: "*The **Eastern Mediterranean Regional office of the World Health Organization**, also known as **EMRO**, is the regional office of the World Health Organization that serves 22 countries and territories in the Middle East, the North Africa, the Horn of Africa and Central Asia. It is one of the WHO's six regional offices around the world*".(146)

Google scholar: Search for scholarly literature on the web, including "peer-reviewed papers, theses, books, preprints, abstracts and technical reports" from a variety of academic publishers, professional societies, preprint repositories and universities.

MEDLINE: "*Medline is a bibliographic database produced by the US National Library of Medicine. It covers worldwide literature published since 1966. Over 4000 journal titles are indexed, in the fields of medicine, nursing, dentistry, veterinary medicine, and health care system and pre-clinical sciences. 70% of the references have an abstract. The Medline database is produced by the NLM but there is a variety of different services providing access*". (145)

PsycINFO: "*PsycINFO is a department of the American Psychological Association (APA). It provides citations to articles in professional journals, conference proceedings, books, reports, dissertations and even important internet sites in psychology and related disciplines, most with abstracts and some citations. Coverage: 1840-present*".(144)

Web of Science: "*Provides access to the content from three Thomson Reuters ISI (Institute for Scientific Information) Citation Databases: Science Citation Index Expanded; Social Sciences Citation Index; Arts & Humanities Citation Index.*
Coverage: 1900-present [Science 1899-, Social Sciences 1900-, Arts & Humanities 1975-]".(144)

Appendix 6: Systematic review search strategy

A. MEDLINE

1. Medication Errors/ae, cl, mt [Adverse Effects, Classification, Methods]
2. "Drug-Related Side Effects and Adverse Reactions"/
3. adverse drug event*.mp.
4. medication error*.mp.
5. Patient Safety/
6. drug safety.mp.
7. medication safety.mp.
8. prescribed medication*.mp.
9. prescribed drug*.mp.
10. Nonprescription Drugs/
11. over the counter medication*.mp.
12. patient error*.mp.
13. medication management.mp.
14. Medication Therapy Management/
15. drug related problem*.mp.
16. medication related problem*.mp.
17. preventable adverse drug event*.mp.
18. preventable adverse event*.mp.
19. potential adverse event*.mp.
20. ((medic* or drug*) adj3 (error* or problem* or event* or safety)).mp.
21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. household*.mp.
23. residence*.mp.
24. residential home.mp.
25. ambulatory care.mp.
26. Outpatients/
27. self care/ or self medication/ or self manage*.mp.

28. After-Hours Care/

29. out of hours medical care.mp.

30. Homebound Persons/

31. home visit.mp.

32. face to face home interview.mp.

33. face to face interview.mp.

34. Primary Health Care/

35. General Practice/

36. Family Practice/

37. Patient-Centered Care/

38. ((home* or house* or community or ambulatory or primary or family or outpatient) adj3 (setting* or context*)).mp.

39. ((after or post) adj2 hospital discharge).mp.

40. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39

41. Epidemiology/

42. Prevalence/

43. Incidence/

44. risk factor*.mp.

45. follow up.mp.

46. cross sectional.mp.

47. cohort.mp.

48. case control.mp.

49. observational.mp.

50. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49

51. 21 and 40 and 50

52. limit 51 to (humans and yr="1990 -2015")

B. EMBASE

1. adverse drug event*.mp.

2. medication error/

3. patient safety/

4. drug safety/

5. medication safety.mp.

6. prescription drug/

7. prescribed medication*.mp.

8. non prescription drug/

9. over the counter medication*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

10. patient error*.mp.

11. medication therapy management/

12. medication management.mp.

13. drug related problem*.mp.

14. medication related problem*.mp.

15. preventable adverse drug event*.mp.

16. preventable adverse event*.mp.

17. potential adverse drug event*.mp.

18. ((medic* or drug*) adj3 (error* or problem* or event* or safety)).mp.

19. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20. household*.mp.

21. residence*.mp.

22. ambulatory care/

23. outpatient care/ or outpatient/

24. self care/

25. self medication/

26. self manage*.mp.

27. after hours care.mp.

28. out of hours medical care.mp.

29. home visit.mp.

30. interview/ or face to face interview.mp.

31. primary health care/

32. general practice/

33. patient centered care.mp. or patient care/

34. family practice.mp.

35. ((after or post) adj2 hospital discharge).mp.

36. ((home* or house* or community or ambulatory or primary or family or outpatient) adj3

(setting* or context*)).mp.

37. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36

38. epidemiology/

39. prevalence/

40. incidence/

41. risk factor*.mp.

42. follow up/

43. observational method/

44. cross-sectional study/ or cross sectional.mp.

45. cohort.mp.

46. case control study/ or case control.mp.

47. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46

48. 19 and 37 and 47

49. limit 48 to (human and yr="1990 -2015")

C. PsycINFO

1. medication error*.mp.

2. adverse drug event*.mp.

3. drug related adverse event*.mp.

4. patient safety.mp.

5. drug safety.mp.

6. medication safety.mp.

7. exp Prescription Drugs/ or exp "Prescribing (Drugs)"/

8. prescribed medication*.mp.

9. exp Nonprescription Drugs/

10. over the counter medication*.mp.

11. patient error*.mp.

12. medication management.mp.

13. medication therapy management.mp.

14. drug related problem*.mp.

15. medication related problem*.mp.

16. preventable adverse event*.mp.

17. preventable adverse drug event*.mp.

18. potential adverse event*.mp.

19. ((medic* or drug*) adj3 (error* or problem* or event* or safety)).mp.

20. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19

21. household*.mp.

22. residence*.mp.

23. residential home.mp.

24. ambulatory care.mp.

25. exp Outpatients/

26. self care.mp.

27. exp Self Medication/

28. exp Self Management/

29. after hours care.mp.

30. home visit.mp.

31. exp Home Visiting Programs/

32. exp Interviews/ or face to face interview.mp.

33. exp Primary Health Care/

34. exp General Practitioners/ or general practice.mp.

35. family practice.mp.

36. patient centered care.mp.

37. ((after or post) adj2 hospital discharge).mp.

38. ((home* or house* or community or ambulatory or primary or family or outpatient) adj3 (setting* or context*)).mp.

39. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38

40. exp Epidemiology/

41. incidence.mp.

42. prevalence.mp.

43. risk factor*.mp.

44. follow up.mp.

45. exp Observation Methods/

46. cross sectional.mp.

47. cohort.mp.

48. case control.mp.

49. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48

50. 20 and 39 and 49

51. limit 50 to (human and yr="1990 -2015")

D. Web of Science

#5	#4 AND #3 AND #2 AND #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015
#4	TS=(follow up) OR TS=(cross sectional) OR TS=(cohort) OR TS=(case control) OR TS=(observational study) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015
#3	TS=(epidemiology) OR TS=(incidence) OR TS=(prevalence) OR TS=(risk factor*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015
#2	**TOPIC:** (household) *OR* **TOPIC:** (residence) *OR* **TOPIC:** (ambulatory) *OR* **TOPIC:** (community) *OR* **TOPIC:** (outpatient) *OR* **TOPIC:** (general practice) *OR* **TOPIC:** (family practice) *OR* **TOPIC:** (primary health care) *OR* **TOPIC:** (patient centered care) *OR* **TOPIC:** (self care) *OR* **TOPIC:** (self manage*) *OR* **TOPIC:** (self medication*) *OR* **TOPIC:** (after hours care) *OR* **TOPIC:** (after hospital discharge) *OR* **TOPIC:** (post hospital discharge) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015
#1	**TOPIC:** (medication error*) *OR* **TOPIC:** (adverse drug event*) *OR* **TOPIC:** (drug related adverse event*) *OR* **TOPIC:** (medication related adverse event*) *OR* **TOPIC:** (patient safety) *OR* **TOPIC:** (drug safety) *OR* **TOPIC:** (patient error*) *OR* **TOPIC:** (drug

	related problem*) *OR* **TOPIC:** (preventable adverse drug event*) *OR* **TOPIC:** (potential adverse drug event*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=1990-2015

E. CINAHL

S25	S21 AND S22 AND S23 Limiters – Published Date: 19900101-20151031
S24	S21 AND S22 AND S23
S23	S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20
S22	S8 OR S9 OR S10 OR S11 OR S12 OR S13
S21	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
S20	(MH "Case Control Studies")
S19	"cohort"
S18	(MH "Cross Sectional Studies")
S17	(MH "Prospective Studies")
S16	(MH "Risk Factors")
S15	(MH "Incidence")
S14	(MH "Prevalence")
S13	(MH "Family Practice") OR "general practice"
S12	(MH "Primary Health Care")
S11	(MH "Self Care")
S10	(MH "Ambulatory Care")
S9	(MH "Outpatients")
S8	"household*"
S7	"medication therapy management"
S6	"drug related problem*"
S5	"over the counter medication*"
S4	"prescribed medication*"

S3	"drug safety"
S2	(MH "Adverse Drug Event")
S1	(MH "Medication Errors")

F. Global Health Library (EMRO)

(Adverse drug event* OR medication error* OR patient error*) AND (outpatient OR ambulatory OR general practice OR family practice OR household OR community OR home visit OR after hospital discharge) AND (prevalence OR incidence OR risk factor* OR cross sectional OR cohort OR case control)

G. Google scholar

(Medication error* OR adverse drug event*) AND (home* OR ambulatory OR community OR outpatient OR general practice OR after discharge) AND (prevalence OR incidence OR risk factor* OR Cross sectional OR cohort OR case control)

2- Experts in the field was contacted by email:

	Date	Replay or not	Result
1- Tahir M khan from Malaysia	11/8/2015	Yes	(Medication error in the Southeast Asian countries) systematic review study
2- Azmi Hassali from Malaysia	11/8/2015	Yes	Referred to Tahir M khan
3- Izham M Ibrahim from Malaysia	11/8/2015	No	-
4- David Bates	11/8/2015	No	-
5- Tejal Gandhi	11/8/2015	No	-
6- Kathleen Walsh	11/8/2015	Yes	Published papers

Appendix 7: Outcome measures and their associated ADEs

	Clinically important errors in medicine management	**Medication error stage**	**Outcome: error-related adverse event or potential adverse event**	**Risk**
Primary outcome measures				
1	Patient with a history of peptic ulcer receiving a non-selective NSAID without PPI cover	Prescribing-contraindication	Serious Gastrointestinal bleeding (GI bleed)	Extreme risk
2a	Patient with a history of asthma who has been prescribed a beta-blocker	Prescribing-contraindication	Serious asthma attack	High risk
3	Patient aged 75 years and older who has been prescribed an angiotensin converting enzyme inhibitor (ACEI) or a loop diuretic long-term who has not had a recorded check of their renal function and electrolytes in the previous 15 months	Inadequate monitoring	Admission to hospital with a serious electrolyte disturbance or dehydration	High risk
Secondary outcome measures				
2b	Patient with a history of asthma [and no history of coronary heart disease	Prescribing-contraindication	Serious asthma attack	High risk

	(CHD)] who has been prescribed a beta-blocker			
4	Woman with a past medical history of venous or arterial thrombosis who has been prescribed a combined hormonal contraceptive (CHC)	Prescribing-contraindication	Venous or arterial thrombosis	High risk
5a +5b	Patient receiving methotrexate for at least three months who has not had a recorded full blood count and / or liver function test within the previous three months	Inadequate monitoring	Serious haematological or liver problem	High risk
6	Patient receiving warfarin for at least three months who has not had a recorded check of their international normalised ratio (INR) within the previous 12 weeks	Inadequate monitoring	Serious bleed associated with high INR, or thromboembolic event associated with low INR	Extreme risk
7	Patient receiving lithium for at least 3 months who has not had a recorded check of their lithium levels within	Inadequate monitoring	Lithium toxicity	High risk

	the previous 3 months			
8	Patient receiving amiodarone for at least 6 months who has not had a thyroid function test within the previous 6 months	Inadequate monitoring	Thyrotoxicosis	High risk
9	Patient receiving prescriptions of methotrexate without instructions that the drug should be taken weekly	Prescribing-dosing problem	Toxic effects from methotrexate overdose	High risk
10	Patient receiving prescriptions of amiodarone for at least one month without instructions to take a dose of 200mg or less per day	Prescribing-dosing problem	Toxic effects from amiodarone overdose	
Composite secondary outcome measures				
11	Patients with at least one prescription problem (a combination of outcome measures 1, 2, or 4)			
12	Patients with at least one monitoring problem (a combination of outcome measures 3, 5, 6, 7, and 8)			

Additional revised updated outcome measures				
13	Prescription of an oral NSAID, without co-prescription of an ulcer-healing drug, to a patient aged ≥65 years	Prescribing-contraindication	GI bleed	
14	Prescription of an anti-platelet drug without co-prescription of an ulcer-healing drug, to a patient with a history of peptic ulceration	Prescribing-contraindication	GI bleed	High risk
15	Prescription of warfarin or New Oral Anti-Coagulant (NOAC) in combination with an oral NSAID	Prescribing-contraindication	GI bleed	High risk
16	Prescription of warfarin or NOAC and an anti-platelet drug in combination without co-prescription of an ulcer-healing drug	Prescribing-contraindication	GI bleed	
17	Prescription of aspirin in combination with another anti-platelet drug without co-prescription of an ulcer-healing drug	Prescribing-contraindication	GI bleed	

18	Prescription of a long-acting beta-2 agonist inhaler (excluding combination products with inhaled corticosteroid) to a patient with asthma who is not also prescribed an inhaled corticosteroid	Prescribing-contraindication	Exacerbation of asthma	High risk
19	Prescription of an oral NSAID to a patient with heart failure	Prescribing-contraindication	Heart failure	High risk
20	Prescription of antipsychotics for >6weeks in a patient aged ≥ 65 years with dementia but not psychosis	Prescribing-contraindication	Stroke	High risk
21	Prescription of an oral NSAID to a patient with estimated Glomerular Filtration Rate (eGFR) < 45	Prescribing-contraindication	Kidney Injury	Extreme risk

(85, 99, 107)

Appendix 8: Pilot and Cohort studies Kappa coefficient agreements between two independent data extractors

Phase 3: Pilot study

The number of positive (error or risk) in the pilot study dataset is 196 in 200 patients. To be able to calculate the kappa coefficient, the data were entered as a two-way table.

To know the result of the kappa coefficient the following command was entered in STATA (version 14):

. kap rater1 rater2 [freq=pop], tab

Where kap is the interrater agreement for two unique raters, freq is frequency, pop is the number assessed by both raters and tab is to show the table of assessment.

```
. kap GA SK [freq=pop], tab

     Data |
  extractor |
     GA's |        Data extractor SK's assessment
assessment |     error   no error       risk    no risk |     Total
-----------+--------------------------------------------+----------
     error |        26          6          0          0 |        32
  no error |         0          0          0          0 |         0
      risk |         0          0        149         15 |       164
   no risk |         0          0          0          0 |         0
-----------+--------------------------------------------+----------
     Total |        26          6        149         15 |       196

           Expected
Agreement  Agreement     Kappa   Std. Err.          Z      Prob>Z
-------------------------------------------------------------------
  89.29%     65.77%    0.6869     0.0545       12.61      0.0000
```

Where GA's is Ghadah Assiri (rater 1), SK is Salma Al-khani (rater 2).

The agreement between the two independent data extractors in the pilot study was substantial (Kappa 0.69). All discrepancies were resolved by discussion and by double-checking the records.

Phase 4: Cohort study

The number of observations with positive (error or risk) in the cohort study dataset is 48 in 200 Patients. The data were entered as a two-way table.

To know the result of the kappa coefficient the following command was entered in STATA (version 14):

. kap rater1 rater2 [freq=pop], tab

Where kap is the interrater agreement for two unique raters, freq is frequency, pop is the number assessed by both raters and tab to show the table of assessment.

```
. kap GA SH [freq=pop], tab
```

Data extractor GA's assessment	Data extractor SK's assessment				
	error	no error	risk	no risk	Total
error	11	1	0	0	12
no error	0	0	0	0	0
risk	0	0	33	3	36
no risk	0	0	0	0	0
Total	11	1	33	3	48

Agreement	Expected Agreement	Kappa	Std. Err.	Z	Prob>Z
91.67%	57.29%	0.8049	0.1230	6.54	0.0000

Where GA's is Ghadah Assiri (rater 1), SH is Sarah Al-hathlool (rater 2).

The agreement between the two independent data extractors in the cohort study for 200 records was substantial (Kappa 0.8). All discrepancies were resolved by discussion and by double-checking the records.

Appendix 9: Feasibility and pilot study ethics (The Clinical Research Committee and Research Ethics Committee of KFSH&RC ethical approval)

مستشفى الملك فيصل التخصصي ومركز الأبحاث
King Faisal Specialist Hospital & Research Centre
Gen. Org. مؤسسة عامة

Office of Research Affairs

☐ **24528** ☐ **27894** ☐ **MBC 03**

INTERNAL MEMORANDUM

TO: Abdallah Alkhenizan, MD
Chairman
Department of Family Medicine/Poly Clinics

DATE: 06 Sha'ban 1438
02 May 2017

THRU: Afshan Ali, MD, MBA
Chairperson, Research Ethics Committee
Office of Research Affairs

REF: ORA/0817/38

FROM: Rana Moslimany, Pharm D, CCRP
Member, Research Ethics Committee
Office of Research Affairs

SUBJECT: Project # 2171 060

Protocol for a Feasibility Study to Inform the Development of a Pilot Retrospective Cohort Study Investigating the Epidemiology of Medication Errors Using Electronic Health Records in Riyadh, Saudi Arabia

Further to ORA's email (dated 19 April 2017), your reply/Waiver of Informed Consent Form (email dated 20 April 2017) was reviewed by the Research Ethics Committee (REC) on 25 April 2017. It is my pleasure to inform you that the REC has accepted the reply as submitted and recommended the proposal, Data Collection Sheet and the Waiver of Informed Consent for approval; and I would like to take this opportunity to congratulate you on behalf of the Research Advisory Council.

Please be informed that in conducting this proposal, the Investigators are required to abide by the rules and regulations of the Government of Saudi Arabia, KFSH&RC, and the RAC. Further, you are required to submit a Progress/Final Report by 25 March 2018; so it can be reviewed by the Committees without lapse of approval. The approval of this proposal will automatically be suspended 25 April 2018, pending the acceptance of the Report. You also need to notify the ORA as soon as possible in the case of:

6. Any amendments to the project,
7. Termination of the study,
8. Any event or new information that may affect the benefit/risk ratio of the proposal.

RM/AA/GH

ORA E-Mail: ora@kfshrc.edu.sa

0817 2171 060 Dr. Abdullah Al Khenizan Approve reply REC

A

C

Please observe the following:

5 Personally identifying data should only be collected when necessary for research.

6 The data collected should only be used for this proposal.

7 Data should be stored securely so that only a few authorised users are permitted access to the database.

8 Secondary disclosures of personally identifiable data are not allowed.

9 Should there be a need to contact the research subjects for follow-up information, you will Need to seek the authorisation of the RAC prior to such contact.

We wish you every success in your research endeavours.

cc: Clinical Research Coordinator, Department of Family Medicine/Poly Clinics RAC File

Appendix 10: Pilot study data collection form

A: demographic and basic information

Patient code				
Age	____ Years			
Gender	M		F	
Nationality	Saudi		Non-Saudi	
Diagnosis or past medical history				
	☐	Anaemia	☐	Back pain
	☐	Allergic rhinitis	☐	Osteoporosis
	☐	Benign prostatic hypertrophy (BPH)	☐	Osteoarthritis
	☐	Bronchial Asthma	☐	Type 1 diabetes mellitus
	☐	Chronic Obstructive Pulmonary Disease (COPD)	☐	Type 2 diabetes mellitus
	☐	Coronary artery disease (CAD)	☐	Vitamin D deficiency
	☐	Depression	☐	Hypertriglyceridemia
	☐	Essential primary hypertension (HTN)	☐	Hyperlipidaemia
	☐	Gastroesophageal reflux disease (GERD)	Other:	
	☐	Heart failure (HF)		
	☐	Hyperthyroidism		
	☐	Hypothyroidism		
Polypharmacy at any point (≥ 5 medications**)**	Yes		No	
OTC medication	Yes		No	

If the patient had a history of the following:	**If the patient was on the following medications**
Peptic ulcer – see (outcome 1 and 14)	Aged ≥ 75 years and on **angiotensin converting enzyme (ACE) inhibitors or diuretics** – see (outcome 3)
Asthma – see (outcome 2a, 18) OR **Asthma and <u>not</u> coronary heart disease (CHD)**—see (outcome 2b, 18)	
A female with **venous or arterial thromboembolism and arterial thrombosis** – see (outcome 4)	**Methotrexate** – see (outcome 5a, 5b & 9)
Patient aged ≥ 65 years – see (outcome 13)	**Warfarin** – see (outcome 6, 15 & 16)
Patient aged ≥ 65 years with dementia – see (outcome 20)	**New Oral Anti-Coagulant (NOAC)** – see (outcome 15 & 16)
Heart failure – see (outcome 19)	**Lithium** – see (outcome 7)
estimated Glomerular Filtration Rate (eGFR) < 45 – see (outcome 21)	**Amiodarone** – see (outcome 8 &10)
	Aspirin – see (outcome 17)

B: outcome measures

	Numerator	Yes/ no	Denominator	Yes/ no	Comment
Primary, secondary and composite outcome measures					
1	History of **peptic ulcer** prescribed an non-steroidal anti-inflammatory drug (NSAID) without a proton-pump inhibitor (PPI)		History of **peptic ulcer** without a PPI		
2a	**Asthma** prescribed a β-blocker		**Asthma**		
2b	**Asthma** and **not CHD** prescribed a β-blocker		**Asthma** and **not CHD**		
3	Aged ≥75 on long term **ACE inhibitors or diuretics** without urea and electrolyte monitoring in the previous 15 months		Aged ≥75 on long term **ACE inhibitors or diuretics**		
4	History of **venous or arterial thromboembolism and arterial thrombosis** prescribed combined oral contraceptives (Female)		History of **venous or arterial thromboembolism and arterial thrombosis** (female)		
5a	**Methotrexate** for ≥ 3 months without a full blood count in last 3 months		**Methotrexate** for ≥ 3 months		
5b	**Methotrexate** for ≥ 3 months without an liver function test in last 3 months		**Methotrexate** for ≥ 3 months		
6	**Warfarin** for ≥ 3 months without an international normalised ratio (INR) in last 3 months		**Warfarin** for ≥ 3 months		
7	**Lithium** for ≥ 3 months without a lithium level in last 3 months		**Lithium** for ≥ 3months		
8	**Amiodarone** for ≥ 6 months without a thyroid function test in the last 6 months		**Amiodarone** for ≥ 6 months		
9	**Methotrexate** without instructions to take weekly		Patient prescribed **methotrexate**		
10	**Amiodarone** for ≥ 1 month at a dose of more than 200mg/day		**Amiodarone** for ≥ 1 month		
11	Patients with at least one prescription problem (a combination of outcome measures 1, 2, or 4)				
12	Patients with at least one monitoring problem (a combination of outcome measures 3, 5, 6, 7, and 8)				
Revised updated outcome measures					
13	Patients **aged ≥65 years** prescribed an oral NSAID without co-prescription of an ulcer-healing drug		Patients **aged ≥65 years** without co-prescription of an ulcer-healing drug		
14	History of **peptic ulcer** prescribed an anti-platelet drug without co-prescription of an ulcer-healing drug		History of **peptic ulceration** without co-prescription of an ulcer-healing drug		
15	Prescribed **warfarin or NOAC** in combination with an oral NSAID		Prescribed **warfarin or NOAC**		
16	Prescribed **warfarin or NOAC** and an anti-platelet drug in combination without co-prescription of an ulcer-healing drug		Prescribed **warfarin or NOAC** without co-prescription of an ulcer-healing drug		
17	Prescribed **aspirin** in combination with another anti-platelet drug without co-prescription of an ulcer-healing drug		Prescribed **aspirin** without co-prescription of an ulcer-healing drug		
18	**Asthma** prescribed a long-acting beta-2 agonist inhaler who is not also prescribed an inhaled corticosteroid		**Asthma** prescribed a long-acting beta-2 agonist inhaler		
19	**Heart failure** prescribed an oral NSAID		**Heart failure**		
20	Patients **aged ≥65 years** with **dementia** but not psychosis prescribed antipsychotic drugs for >6weeks		Patients **aged ≥65 years** with **dementia** but not psychosis		
21	Patients with an **eGFR <45** prescribed an oral NSAID		Patients with an **eGFR <45**		

Abbreviations: NSAID=non-steroidal anti-inflammatory drug. PINCER=pharmacist-led information technology intervention. ACE=angiotensin converting enzyme. PPI=proton-pump inhibitor. CHD=coronary heart disease. INR=international normalised ratio. eGFR=estimated Glomerular Filtration Rate. NOAC=New Oral Anti-Coagulant.

Appendix 11: The RECORD statement – checklist of items, extended from the STROBE statement that should be reported in observational studies using routinely collected health data. (Pilot study)

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	102	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the	102

				study, this should be clearly stated in the title or abstract.	
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	102		
Objectives	3	State specific objectives, including any prespecified hypotheses	47		
Methods					
Study Design	4	Present key elements of study design early in the paper	103		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	103		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the	103	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.	103

		eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	105	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	

Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	106		
Bias	9	Describe any efforts to address potential sources of bias	107		
Study size	10	Explain how the study size was arrived at	107		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	109		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were	109		

		addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	108

Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	-
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	115	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential	115		

		confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	117		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were	124		

		adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	124		
Discussion					
Key results		Summarise key results with reference to study objectives	164		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	167	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing	

				data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	169		
Generalisability	21	Discuss the generalisability (external validity) of the study results	168		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			
Accessibility of protocol, raw data, and programming				RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or	-

code				programming code.	

From: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press. *Checklist is protected under Creative Commons Attribution (CC BY) license.

Appendix 12: Cohort study data collection sheet

A: demographic and basic information

Patient characteristics				
Patient code				
Age	____ Years			
Gender	M		F	
Nationality	Saudi		Non-Saudi	
Diagnosis or past medical history				
		Anaemia		Back pain
		Allergic rhinitis		Osteoporosis
		Benign prostatic hypertrophy (BPH)		Osteoarthritis
		Bronchial Asthma		Type 1 diabetes mellitus
		Chronic Obstructive Pulmonary Disease (COPD)		Type 2 diabetes mellitus
		Coronary artery disease (CAD)		Vitamin D deficiency
		Depression		Hypertriglyceridemia
		Essential primary hypertension (HTN)		Hyperlipidaemia
		Gastroesophageal reflux disease (GERD)	Other:	
		Heart failure (HF)		
		Hyperthyroidism		
		Hypothyroidism		
Polypharmacy at any point (≥ 5 medications**)**	Yes		No	
OTC medication	Yes		No	

Physician characteristics	
Physician code	
Physician number	

If the patient had a history of the following:	**If the patient was on the following medications**
Peptic ulcer – see (outcome 1 and 14) **Asthma** – see (outcome 2a, 18) OR **Asthma and <u>not</u> coronary heart disease (CHD)**—see (outcome 2b, 18) A female with **venous or arterial thromboembolism and arterial thrombosis** – see (outcome 4) **Patient aged ≥ 65 years** – see (outcome 13) **Patient aged ≥ 65 years with dementia** – see (outcome 20) **Heart failure** – see (outcome 19) **eGFR < 45** – see (outcome 21)	Aged ≥ 75 years and on **angiotensin converting enzyme (ACE) inhibitors or diuretics** – see (outcome 3) **Methotrexate** – see (outcome 5a, 5b & 9) **Warfarin** – see (outcome 6, 15 & 16) **New Oral Anti-Coagulant (NOAC)** – see (outcome 15 & 16) **Lithium** – see (outcome 7) **Amiodarone** – see (outcome 8 &10) **Aspirin** – see (outcome 17)

B: outcome measures

	Numerator	Yes/no	Denominator	Yes/no	Comment
Primary, secondary and composite outcome measures					
1	History of **peptic ulcer** prescribed an non-steroidal anti-inflammatory drug (NSAID) without a proton-pump inhibitor (PPI)		History of **peptic ulcer** without a PPI		
2a	**Asthma** prescribed a β-blocker		**Asthma**		
2b	**Asthma** and **not CHD** prescribed a β-blocker		**Asthma** and **not CHD**		
3	Aged ≥75 on long term **ACE inhibitors or diuretics** without urea and electrolyte monitoring in the previous 15 months		Aged ≥75 on long term **ACE inhibitors or diuretics**		
4	History of **venous or arterial thromboembolism and arterial thrombosis** prescribed combined oral contraceptives (Female)		History of **venous or arterial thromboembolism and arterial thrombosis** (female)		
5a	**Methotrexate** for ≥ 3 months without a full blood count in last 3 months		**Methotrexate** for ≥ 3 months		
5b	**Methotrexate** for ≥ 3 months without an liver function test in last 3 months		**Methotrexate** for ≥ 3 months		
6	**Warfarin** for ≥ 3 months without an international normalised ratio (INR) in last 3 months		**Warfarin** for ≥ 3 months		
7	**Lithium** for ≥ 3 months without a lithium level in last 3 months		**Lithium** for ≥ 3months		
8	**Amiodarone** for ≥ 6 months without a thyroid function test in the last 6 months		**Amiodarone** for ≥ 6 months		
9	**Methotrexate** without instructions to take weekly		Patient prescribed **methotrexate**		
10	**Amiodarone** for ≥ 1 month at a dose of more than 200mg/day		**Amiodarone** for ≥ 1 month		
11	Patients with at least one prescription problem (a combination of outcome measures 1, 2, or 4)				
12	Patients with at least one monitoring problem (a combination of outcome measures 3, 5, 6, 7, and 8)				
Revised updated outcome measures					
13	Patients **aged ≥65 years** prescribed an oral NSAID without co-prescription of an ulcer-healing drug		Patients **aged ≥65 years** without co-prescription of an ulcer-healing drug		
14	History of **peptic ulcer** prescribed an anti-platelet drug without co-prescription of an ulcer-healing drug		History of **peptic ulceration** without co-prescription of an ulcer-healing drug		
15	Prescribed **warfarin or NOAC** in combination with an oral NSAID		Prescribed **warfarin or NOAC**		
16	Prescribed **warfarin or NOAC** and an anti-platelet drug in combination without co-prescription of an ulcer-healing drug		Prescribed **warfarin or NOAC** without co-prescription of an ulcer-healing drug		
17	Prescribed **aspirin** in combination with another anti-platelet drug without co-prescription of an ulcer-healing drug		Prescribed **aspirin** without co-prescription of an ulcer-healing drug		
18	**Asthma** prescribed a long-acting beta-2 agonist inhaler who is not also prescribed an inhaled corticosteroid		**Asthma** prescribed a long-acting beta-2 agonist inhaler		
19	**Heart failure** prescribed an oral NSAID		**Heart failure**		
20	Patients **aged ≥65 years** with **dementia** but not psychosis prescribed antipsychotic drugs for >6weeks		Patients **aged ≥65 years** with **dementia** but not psychosis		
21	Patients with an **eGFR <45** prescribed an oral NSAID		Patients with an **eGFR <45**		

Abbreviations: NSAID=non-steroidal anti-inflammatory drug. PINCER=pharmacist-led information technology intervention. ACE=angiotensin converting enzyme. PPI=proton-pump inhibitor. CHD=coronary heart disease. INR=international normalised ratio. E GFR=estimated Glomerular Filtration Rate. NOAC=New Oral Anti-coagulant.

Appendix 13: Cohort study ethics

مستشفى الملك فيصل التخصصي ومركز الأبحاث
King Faisal Specialist Hospital & Research Centre
Gen. Org. مؤسسة عامة
Office of Research Affairs
☎24528 🖷 27894 ✉MBC 03

INTERNAL MEMORANDUM

TO: Abdullah AlKhenizan, MD
Chairman
Department of Family Medicine

DATE: 17 Shawwal 1438
11 July 2017

FROM: Ammar Al Kawi, MD, FAAN, FACP
Deputy Chairman, Research Ethics Committee
Office of Research Affairs

REF: ORA/1087/38

SUBJECT: Project #2171 060 - "Amendment Request"
Protocol for a Feasibility Study to Inform the Development of a Pilot Retrospective Cohort Study Investigating the Epidemiology of Medication Errors Using Electronic Health Records in Riyadh, Saudi Arabia

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The Amendment request (Ref: FMPC/907/38 received by the Office of Research Affairs on 03 July 2017) related to the above- referenced project was reviewed by the Research Ethics Committee (REC) on 05 July 2017.

The REC recommended the acceptance of Amendment as submitted.

Please note that the Progress/Final Report due on **25 March 2018**. The Report should be reviewed and accepted by the Committees before **25 April 2018** (as per ORA/0817/38, attached).

Thank you

Att. a/s

cc: RAC File

/mk/ap/
ORA
A
C

E-mail : ...@kfshrc.edu.sa

مستشفى الملك فيصل التخصصي ومركز الأبحاث
King Faisal Specialist Hospital & Research Centre
Gen. Org. مؤسسة عامة

RESEARCH ETHICS COMMITTEE

MBC: , Ext: 32939 , Fax: Click to edit

INTERNAL MEMO

TO: **Abdullah Alkhenizan, MD**
Chairman, Family Medicine/Polyclinics
Family Medicine & Polyclinics Department - Riyadh

DATE: 22 Rabia Al Awal 1439
10 December 2017

THRU: **Afshan Ali**
Chairman
Research Ethics Committee

REF: C380/151/39

FROM: **Ammar Alkawi**
Member
Research Ethics Committee

SUBJECT: **PROJECT # 2171060 - PROTOCOL FOR A FEASIBILITY STUDY TO INFORM THE DEVELOPMENT OF A PILOT RETROSPECTIVE COHORT STUDY INVESTIGATING THE EPIDEMIOLOGY OF MEDICATION ERRORS USING ELECTRONIC HEALTH RECORDS IN RIYADH, SAUDI ARABIA**

Your request (ref: FMPC/179/39 dated 23 November 2017) to amend the above-referenced project to include physician-related risk factors was reviewed by the Research Ethics Committee on 02 December 2017.

It is my pleasure to inform you that the Committee has recommended the request for approval as submitted.

Please note that the Progress Report for this project is due by 25 April 2018.

thank you.

AK/ahs

Appendix 14: The RECORD statement – checklist of items, extended from the STROBE statement that should be reported in observational studies using routinely collected health data. (Cohort study)

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	129	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in	129

				the title or abstract.	
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	129		
Objectives	3	State specific objectives, including any prespecified hypotheses	47		
Methods					
Study Design	4	Present key elements of study design early in the paper	129		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	129		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources	130	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies	130

		and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	132	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	
Data sources/	8	For each variable of interest, give	132		

measurement		sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			
Bias	9	Describe any efforts to address potential sources of bias	133		
Study size	10	Explain how the study size was arrived at	133		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	134		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed	134		

		(d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	134
Linkage		..		RECORD 12.3: State whether the	-

				study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	135	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	135
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders	135		

		(b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	137		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were	150		

		included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	151		
Discussion					
Key results	18	Summarise key results with reference to study objectives	164		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	168	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over	

				time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	170		
Generalisability	21	Discuss the generalisability (external validity) of the study results	168		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			
Accessibility of protocol, raw data, and programming code				RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	--

From: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press. *Checklist is protected under Creative Commons Attribution (CC BY) license.

Appendix 15: Research output

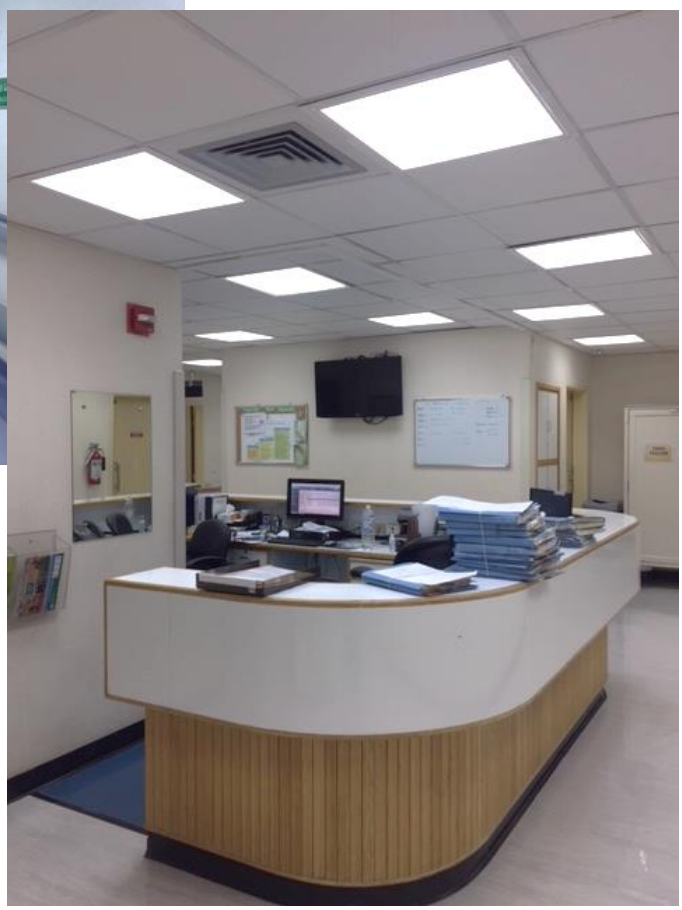
1. Assiri G, Grant L, Aljadhey H, Sheikh A. Investigating the epidemiology of medication errors and error-related adverse drug events (ADEs) in primary care, ambulatory care and home settings: a systematic review protocol. BMJ Open. 2016; 6 (8).
2. Assiri G, Shebl N, Mahmoud M, Aloudah N, Grant E, Aljadhey H, Sheikh A. Investigating the Epidemiology of Medication Errors and Error-related Adverse Drug Events in Adults in Primary Care, Ambulatory Care and Home Settings: a Systematic Review. Poster presented at: 10th medication safety conference. Integrating healthcare systems and patient engagement; 2017 Oct 27-29; Abu-Dhabi, United Arab Emirates.
3. Assiri G, Shebl N, Mahmoud M, Aloudah N, Grant E, Aljadhey H, Sheikh A. What is the epidemiology of medication errors, error-related adverse events and risk factors for errors in adults managed in community care contexts? A systematic review of the international literature. BMJ Open. 2018; 8: e019101.
4. Assiri G, Al-Khenizan A, Al-Khani S, Grant E, Sheikh A. Investigating the Epidemiology of Medication Errors in Adults in Community Care Settings: a Retrospective Cohort Study in Riyadh, Saudi Arabia. Saudi Medical Journal. 2019; 40(2):158-167.
5. Assiri G, Al-Khenizan A, Al-Khani S, Grant E, Sheikh A. Investigating the Epidemiology of Medication Errors in Adults in Community Care Settings: a Retrospective Cohort Study in Riyadh, Saudi Arabia. Poster presented at: 4th Global Ministerial Patient Safety Summit; 2019 March 02; Jeddah, Saudi Arabi

Appendix 16: Fieldwork figures

KFSH&RC outpatient clinic entrance

KFSH&RC Family Medicine and Polyclinics level

KFSH&RC Family Medicine and Polyclinics entrance



KFSH&RC Family Medicine and Polyclinics nurse station